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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : **C07D 491/22, A61K 31/47**	**A1**	**(11) International Publication Number:** **WO 98/07727** **(43) International Publication Date:** 26 February 1998 (26.02.98)

(21) International Application Number: PCT/GB97/02205

(22) International Filing Date: 15 August 1997 (15.08.97)

(30) Priority Data:
60/024,171 19 August 1996 (19.08.96) US

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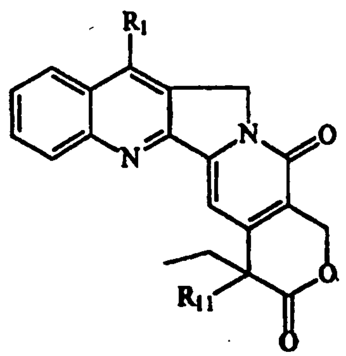
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: HIGHLY LIPOPHILIC CAMPTOTHECIN DERIVATIVES



(I)

(57) Abstract

Compounds having formula (I), wherein R_1 is acyl of formula -C(O)R_2 wherein R_2 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or aryl; or R_1 is C_{2-8} alkenyl or C_{2-8} alkynyl, each of which is optionally substituted by one or more halogen atoms, hydroxy groups, C_{1-6} alkyl or C_{1-6} alkoxy groups; or R_1 is halo; oxo, in which case the 1,2- and 6,7-ring double bonds are replaced by a single 2,6-ring double bond; or -S-R_3, wherein R_3 is C_{1-6} alkyl, aryl or halo- or C_{1-6} alkyl-substituted aryl; or R_1 is -S(O)-C_{1-6} alkyl; -OSO_2CF_3; or -$SiR_8R_9R_{10}$, -R_5-$SiR_8R_9R_{10}$ or -S-R_5-$SiR_8R_9R_{10}$ wherein R_5 is C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene and each of R_8, R_9 and R_{10} is individually hydrogen or C_{1-6} alkyl; and R_{11} is hydrogen, hydroxy or a hydroxy-protecting group which protects the hydroxy group against triflylation; in the form of the free bases or pharmaceutically acceptable acid addition salts thereof are highly lipophilic, lactone stable, do not require metabolic activation, and are anti-neoplastic compounds.

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HIGHLY LIPOPHILIC CAMPTOTHECIN DERIVATIVES

FIELD OF THE INVENTION

This invention relates to derivatives of the anti-neoplastic agent camptothecin (CPT).

BACKGROUND OF THE INVENTION

Of the diverse group of substituted CPT derivatives undergoing human clinical development, Irinotecan (CPT-11),7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin, has been one of the most extensively studied in Phase I and Phase II clinical trials in human patients with cancer. It is noteworthy that Irinotecan, which is a water-soluble prodrug, is biologically inactive and requires activation by a putative carboxylesterase enzyme. The active species of Irinotecan is the depiperidinylated derivative, 10-hydroxy-7-ethyl camptothecin (SN38: Miyasaka et al. U.S. Patent 4,473,692). SN38 is a toxic lipophilic metabolite which is formed by an in vivo bioactivation of Irinotecan by a putative carboxylesterase enzyme.

SN38 is very poorly soluble in water and has not been directly administered to human patients with cancer. Recently, it has been reported in human patients that SN38 undergoes further metabolism to form a glucuronide species which is an inactive form of the drug with respect to antitumor activity, and also appears to be involved in producing human toxicity (diarrhea, leukopenia) and substantial interpatient variability in drug levels of the free metabolite and its glucuronide.

Irinotecan has been tested in human clinical trials in the United States, Europe and Japan. Nearly 100 patient deaths directly attributable to Irinotecan drug toxicity have been reported in Japan alone. The Miyasaka et al. U.S. Patents 4,473,692 and 4,604,463 state that the object of their invention is to "provide 10-substituted camptothecins which are strong in anti-tumor

activity and possess good absorbability in living bodies with very low toxicity" and "to provide new camptothecin derivatives which are strong in anti-tumor activity and possess good solubility in water and an extremely low toxicity".

Having multiple drug-related human deaths and serious patient toxicity, is clearly a failure of the Miyasaka et al. inventions to fulfil their stated objects. It is notable that tremendous interpatient variability with regard to drug levels of various forms, drug metabolism, certain pharmacokinetic properties and toxicity has been reported with the use of Irinotecan in human subjects with cancer. Parenteral administration of Irinotecan can achieve micromolar plasma concentrations of Irinotecan that, through metabolism to form SN38, can yield nanomolar concentrations of the active metabolite SN38. It has recently been reported in human subjects that SN38 undergoes further metabolism to form the SN38 glucuronide (Gupta et al. "Metabolic Fate of Irinotecan in Humans: Correlation of Glucuronidation with Diarrhea", Cancer Research 54:3723-3725, 1994).

This further metabolic conversion of Irinotecan is important, since there is also reportedly large variability in the conversion of Irinotecan to SN38 and large interpatient variability in the metabolism of SN38 to form the inactive (and toxic) SN38 glucuronide in human subjects. (Gupta et al., loc. cit. and Ohe, Y. et al., "Phase I Study and Pharmacokinetics of CPT-11 with 5-Day Continuous Infusion", JNCI 84(12):972-974, 1992).

Since the amount of Irinotecan and SN38 metabolized is not predictable in individual patients, significant clinical limitations are posed and create the risk of life-threatening drug toxicity, and/or risk of drug inactivity due to five possible mechanisms: (1) conversion of greater amounts of Irinotecan to SN38; (2)

inactivation of SN38 by glucuronidation; (3) conversion of SN38 glucuronide to free SN38; (4) lack of anti-neoplastic activity due to the conversion of lesser amounts of Irinotecan to form SN38; and (5) lack of anti-neoplastic activity by more rapid and extensive conversion of SN38 to form the glucuronide species. It is important to note that even a doubling of the plasma concentration of the potent Irinotecan metabolite SN38 may result in significant toxicity, because free SN38 exhibits anti-neoplastic activity at nanomolar concentrations.

Another source of interpatient variability and toxicity is the in vivo de-glucuronidation of SN38 and similar CPT derivatives to produce a free and active species of the drug. Deglucuronidation of a CPT derivative which is susceptible to A-ring glucuronidation, such as SN38, results in an increase in the plasma or local tissue concentration of the free and active form of the drug, and if high enough levels are reached, patient toxicity, and even death may result.

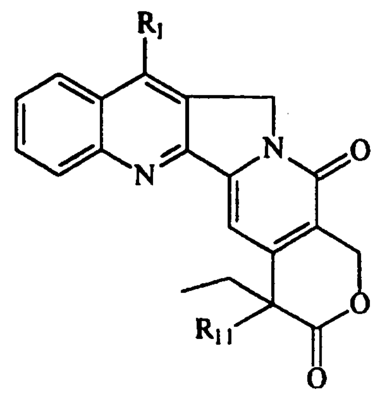
It has been a problem to find CPT derivatives which will not undergo extracyclic A-ring or B-ring glucuronidation and thus be susceptible to deglucuronidation.

SUMMARY OF THE INVENTION

The present invention solves this problem by providing CPT derivatives which have significant utility as highly efficacious anti-neoplastic drugs, and are significantly less toxic than the prior art CPT derivatives. They do not undergo A-ring or B-ring glucuronidation (and implicitly deglucuronidation), and they are not prodrugs requiring metabolic activation. Further, being highly lipophilic, they can be administered directly in the active lactone form and will

have superior bioavailability relative to water-soluble CPT derivatives.

The compounds of the present invention are of formula



(I)

wherein:

- R_1 is acyl of formula $-C(O)R_2$ wherein R_2 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or aryl; or R_1 is C_{2-8} alkenyl or C_{2-8} alkynyl, each of which is optionally substituted by one or more halogen atoms, hydroxy groups, C_{1-6} alkyl or C_{1-6} alkoxy groups; or R_1 is halo; oxo, in which case the 1,2- and 6,7-ring double bonds are replaced by a single 2,6-ring double bond; or $-S-R_3$, wherein R_3 is C_{1-6} alkyl, aryl or halo- or C_{1-6} alkyl-substituted aryl; or R_1 is $-S(O)-C_{1-6}$ alkyl; $-OSO_2CF_3$; or $-SiR_8R_9R_{10}$, $-R_5-SiR_8R_9R_{10}$ or $-S-R_5-SiR_8R_9R_{10}$ wherein R_5 is C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene and each of R_8, R_9 and R_{10} is individually hydrogen or C_{1-6} alkyl; and
- R_{11} is hydrogen, hydroxy or a hydroxy-protecting group which protects the hydroxy group against triflylation;

in the form of the free bases or pharmaceutically acceptable acid addition salts thereof.

The compounds of formula I wherein R_1 is oxo or triflyloxy (trifluoromethanesulfonyloxy) and/or those wherein R_{11} is a hydroxy-protecting group, e.g. acetoxy, are also particularly useful as intermediates in the preparation of the other compounds of formula I, which are the preferred active compounds.

The present invention is also aimed at overcoming other important limitations in bioavailability/pharmacokinetics and common tumor mediated drug resistance mechanisms observed with the use of water-soluble camptothecins or 9-amino or 9-nitro substituted camptothecins as anti-cancer agents. The active new C-7 substituted CPT lactone compounds of this invention have greater clinical utility for treating patients with cancer based on several chemical and pharmacological properties.

First, the direct administration of these highly lipid-soluble camptothecins will result in clinical advantages over other CPT derivatives because of relatively superior tissue penetration, bioavailability and tissue retention. In many instances, it is more useful and convenient to administer the drug orally to cancer patients, and the superior lipid solubility and small molecular size of the active CPT derivatives of this invention will have a great advantage over water-soluble CPT derivatives in the setting of oral (and topical) administration.

The active CPT derivatives of the present invention represent a new class of anti-neoplastic compounds that do not require metabolic activation and have exhibited potent anti-neoplastic activity against common types of cancer including but not limited to cancers of the lung, breast, prostate, pancreas, head and neck, ovary, melanoma and colon. They possess Topoisomerase I inhibitory activity similar to that of other CPT

derivatives but have significant structural modifications giving superior active site binding capability and tissue penetration and avoiding the untoward metabolism and drug resistance mechanisms which are common in human and other mammalian neoplasms.

Until now, lipophilic CPT derivatives with poor water solubility have not been pursued because of limitations in pharmaceutical formulations and methods of use. The active CPT derivatives of the invention can be readily formulated in a pharmaceutically acceptable manner by dissolving the drug composition in an organic solvent or a mixture of organic solvents which have a high degree of physiological safety, thus allowing the direct administration of these new classes of compounds as active species to cancer patients.

In view of very limited number of potentially active CPT derivatives in the poorly water-soluble and highly lipid soluble category, there clearly remains a large unmet need to develop potent, new, poorly water-soluble, highly lipophilic camptothecins which do not require metabolism to an active species and are less susceptible to metabolic inactivation and clinically important types of drug resistance. The active new compounds of the present invention address these unmet needs to an important extent.

The chemical modifications of the CPT scaffold to the derivatives of the invention can be broadly classified as via total synthesis (Comins, D. et al. and Danishefsky, S. J. et al. and references cited therein) or by efficient semi-synthetic approaches utilizing relatively inexpensive and readily available precursors.

Thus, the present invention has provided new chemical substitutions which, particularly when related to the 20(S) CPT molecule or to a 20(S)-rich 20(RS) CPT mixture, can impart the following characteristics:

1. Potent antitumor activity (nanomolar or subnanomolar activity in inhibiting the growth of human and animal tumor cells in vitro);

2. Potent inhibition of Topoisomerase I;

3. Lack of susceptibility to MDR/MRP drug resistance;

4. No metabolic drug activation required;

5. Lack of A-ring or B-ring glucuronidation;

6. Can be administered in the lactone species directly to patients for the purpose of treating a variety of neoplasms;

7. Small molecular weight (e.g. MW <600);

8. Highly soluble in organic pharmaceutical solvents or co-solvents (e.g. propylene glycol, PEG 300-400, dimethyl acetamide, dimethyl isosorbide, N-methyl pyrrolidinone); and

9. Can be administered orally, in addition to parenterally and topically, to subjects with cancer.

Miyasaka et al. (U.S. Patent 4,399,282) state: "As camptothecin itself carries a lactone ring as ring E, this lactone ring is opened by the action of an alkaline reagent, Similary, when the camptothecin derivatives of the present invention are treated, for example with an alkali metal hydroxide or carbonate in a conventional manner at room temperature or at an elevated temperature, the derivatives can be converted into corresponding alkali metal salt such as the sodium, potassium or lithium salt. These salts are all water-soluble and are of course involved in the scope of this invention. These salts are easily converted again into the free form by the action of an acid or in vivo. Thus, the pharmacological effect of the camptothecin derivatives is not influenced by such treatments. A preferable salt of the camptothecin derivative is the sodium or potassium salt."

The inventors submit that this teaching by Miyasaka et al. is incorrect with respect to CPT derivatives possessing an unmodified 20(S) E-ring lactone, since the pharmacological behavior and anti-neoplastic activity of the CPT derivatives will be profoundly and adversely influenced by such treatments, as follows. By treating camptothecins with alkali metal hydroxides or carbonates, the CPT derivative will form the CPT carboxylate species by base-mediated hydrolysis of the E-ring lactone. The resulting CPT derivative carboxylate species will be water-soluble and have substantially reduced anti-neoplastic activity and adversely altered pharmacokinetic and/or drug distribution behavior, and is not the preferred form of the drug. The inventors submit that the lactone E-ring species of CPT (and its derivatives) is the preferred form of the drug for administration to subjects with cancer.

Further, there will be a difference in the pharmacological properties and behavior of the intact lactone E-ring species versus the carboxylate species of camptothecin derivative in vivo in subjects. The carboxylate species of the camptothecin derivative has a significantly shorter plasma half life and exhibits greater toxicity than the lactone species. This is supported by pharmacological evidence from clinical studies in humans and other mammalian species receiving sodium camptothecin, 9-aminocamptothecin and Topotecan (Supko and Malspeis, "Pharmacokinetics of the 9-Amino and 10,11-Methylenedioxy Derivatives of Camptothecin in Mice", Cancer Research 53:3062-3069, 1993; Haas et al. Phase I/Pharmacokinetic Study of Topotecan by 24-Hour Continuous Infusion Weekly", Cancer Research 54:1220-1226, 1994).

Since water-soluble forms of a drug do not penetrate lipid membranes of tissues as well as lipid-soluble drugs, the carboxylate species of CPT derivatives are predicted to have lower bioavailability than CPT derivatives which have the lactone E-ring. Lower bioavailability of the drug will lead to a reduction in the effectiveness of treatment and may increase the risk of patient toxicity.

This invention also teaches new convergent and efficient chemical syntheses of these novel substituted CPT derivatives using commercially available and relatively inexpensive natural isolates of CPT.

Accordingly, a number of new B-ring modifications are taught in this invention. More specifically, the C-7 position of the B-ring is one of the preferred sites of chemical modification using new chemical substituents which impart useful pharmacological, biological and chemical properties to these new compositions of matter.

Certain lipophilic substitutions at the C-7 position of CPT incorporate chemical groups via Minisci-type free radical alkylations on a protonated CPT or on modified substrates. Minisci-type regiospecific alkylations permit the creation of a one-carbon-fewer alkyl chain with respect to the starting aldehyde or alcohol or carboxylic acid. The reaction mechanism suggests that in the case of an aldehyde the introduction of such a side chain occurs <u>via</u> an <u>in situ</u> decarbonylation with concomitant evolution of carbon monoxide.

Other synthetic strategies aiming to anchor lipophilic moieties have been rarely attempted. They have many stages, require the usage of poorly water-soluble compounds or due to the fact that nitrogen-containing heterocycles normally demand drastic reaction conditions for electrophilic substitutions, such as

Friedel Crafts alkylations or acylations and Vilsmier-Haack reactions.

The present invention teaches a novel process of regiospecific homolytic acylation of CPT and CPT derivatives at the C-7 position based on a Minisci-type reaction. Modification to this reaction permits the stabilization of the transient acyl radical that enables one to acylate the CPT skeleton in high yield. The present invention also describes novel processes to furnish certain key versatile synthons for making transformations at the C-7 position.

The invention also provides for pharmaceutical formulations of the compounds of formula I, in association with one or more pharmaceutically acceptable diluents, carriers or excipients. Of course, they must be safe for use with patients, and not affect the efficacy of the active drug ingredient.

The invention also provides methods of treatment of several types of neoplasms, comprising the administration of an effective amount of one of the active compounds of this invention to a patient suffering from one of the indicated diseases. It further includes these compounds for use in treating cancers, as well as their use in the preparation of a medicament for that purpose.

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DESCRIPTION OF THE PREFERRED EMBODIMENTS

Definitions

"Scaffold" means the fixed part of the molecule of formula I, i.e. a CPT in which the 7-position is unsubstituted and normally has the same stereochemistry at the 20-position as 20(S)CPT or a 20(RS)CPT mixture;

"C_x-C_y" alkyl (alkoxy, alkenyl, alkynyl) means a straight or branched-chain alkyl (alkoxy, alkenyl, alkynyl) containing from x to y carbon atoms. Thus, "C_1-C_6 alkyl" (also referred to as "lower alkyl") means a

straight or branched chain alkyl with no more than 6 total carbon atoms.

"C_x-C_y alkenyl" (and, similarly "C_x-C_y alkynyl") means a straight or branched chain hydrocarbyl with at least one double bond (alkenyl) or triple bond (alkynyl) between two of the carbon atoms.

"C_x-C_y alkylene", "C_x-C_y alkenylene" and "C_x-C_y alkynylene" are bivalent forms of the above alkyl, alkenyl and alkynyl groups.

"halogen" or "halo" means chloro, fluoro, bromo or iodo.

"acyl" means -C(O)-R_2, where R_2 is C_1-C_6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or aryl; and

"aryl" means an aromatic carbocyclic ring group of one or more rings.

Examples of the above moieties are as follows:

C_1-C_6 alkyl includes methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, amyl and hexyl; similarly, C_1-C_6 alkoxy includes methoxy...hexyloxy;

similarly, C_1-C_6 alkylene includes methylene, 1,1- and 1,2-ethylene, 1,1- 1,2- and 1,3-propylene, the butylenes, pentylenes and hexylenes;

C_2-C_8 alkenyl(ene) or alkynyl(ene) is preferably C_2-C_6 alkenyl(ene) or alkynyl(ene) and includes vinyl(ene), propenyl(ene), butenyl(ene), acetylenyl(ene), also known as ethynyl(ene), propynyl(ene), and other like moieties with double or triple bonds; and

acyl includes acetyl, propionyl and others;

aryl includes phenyl and naphthyl, as well as substituted variants wherein at least one of the hydrogen atoms bonded to the ring atom is substituted by a halogen atom (e.g. 4-halophenyl) or by a C_1-C_6 alkyl group.

Preferably R_8, R_9 and R_{10} are all methyl, resulting in a trimethylsilyl group, which is preferably joined to

the camptothecin scaffold directly or via a $-CH_2-$, $-CH_2CH_2-$, -CH=CH- or a -C(triple bond)C- group.

C-7 Acylation of protonated camptothecin

Acylation of the heteroaromatic bases such as camptothecins is a problem of great synthetic interest due to the fact that electrophilic aromatic substitutions are generally ineffective with these types of heterocyclic systems. Further, the high reactivity and selectivity of the C-7 position of camptothecin due to increased nucleophilicity under acidic conditions would provide the desired products with minimal unwanted by-products. The respective acyl radicals without the elimination of a C_1 unit can be best obtained from the corresponding aldehydes in the presence of excess trifluoroacetic acid at low temperature. Minisci type alkylation procedures (Minisci, F. , 1973) were found extremely effective with various camptothecin derivatives. However, such alkylations conventionally install a carbon chain or unit that is one carbon fewer than in the starting material. The present invention teaches a modified Minisci type reaction that permits the desired homolytic carbon chain generation as a determinant based upon the type of aldehyde used in the reaction medium. These types of homolytic substitutions are widely accepted as an alternate tool for heterocyclic systems where classical Friedel-Crafts reactions cannot be effectively performed. In principle, the more stable the carbonium ion is the more nucleophilic will be the corresponding radical.

Therefore, almost all the electrophilic species that are useful in the Friedel-Crafts reaction can be utilized, as the corresponding radicals, for the selective substitution of the heteroaromatic bases. This opens a wide variety of organic compounds as radical sources for C-7 substitution of camptothecin. Those

types of compounds include: alkanes, alkenes, alkylbenzenes, alkyl halides, alcohols, ethers, aldehydes, ketones, carboxylic acids, amines, amides, oxaziridines, N-chloramines etc. The major determinants of the reaction conditions that lead to either the desired alkylated product or acylated product are largely controlled by the type of acid present in excess and the free radical initiator.

C-7 Halogenation

The preferred C-7 halo groups are chloro and bromo. Chlorination and bromination at the C-7 position of camptothecin are best done on an electron-deficient nitrogen- bearing camptothecin skeleton. It is evident from the literature that the oxide function at N^1 position of a quinoline moiety could generate substantial nucleophilicity to the α and γ positions of the heterocylic base. Such effects would be enhanced further upon a protonation event on the N-1 oxide. In the case of the camptothecin scaffold, an absolute γ selectivity is envisioned as the α positions are already blocked. The inventors observed that such nucleophilic halogenation proceeds smoothly and selectively on 20-O-acetyl-camptothecin-1-oxide in presence of excess trihalophosphine oxide at 40° C. The camptothecin derivatives thus prepared are subsequently utilized as synthons for cross-coupling reactions as stated below.

Stille type coupling at the C-7 position

Stille's procedure (Stille, J. K., 1986; Stille J. K., 1987) provides one of the most useful methods to construct carbon-carbon bonds. The reaction is catalyzed by organometallic reagents derived from group IA metals via coupling of organic electrophiles and organostannanes in presence of lithium halide.

Similar cross-coupling where boronic acids or esters are employed in place of organostannanes are called the

Suzuki cross-coupling reaction (George B. S., 1994). Excess stoichiometric amounts of lithium chloride are essential for the completion of the reaction as lithium chloride is consumed for the formation of tributyltin chloride and lithium triflate. A variety of organic electrophiles is used in the cross-coupling reaction, of which bromides, iodides and triflates have been extensively studied (Ritter K., 1993). The rate of the reaction can be modulated readily based on the composition and concentration of the organic electrophile. A better understanding of the mechanistic aspects of the rate-limiting transmetallation process led to the recent developments involving the use of cocatalytic Cu(I) and Pd(0) species in this coupling reaction. The role of the Cu(I) species has been envisioned (Liebeskind, 1990) in Sn/Cu transmetallation.

The resulting organocopper species would then transmetallate onto Pd(II) at a higher rate than the stannane itself. This is currently known as the "copper effect." The scope of the reaction is extremely wide. A large number of structurally varied organic groups including vinyl, alkyl, allyl, aryl, acetylenic, amino, amido and (trimethylsilyl)methyl moieties on tin could easily be transferred onto aryl and heteroaryl skeletons, displacing the vinyl triflate or unsaturated halides in high yields. However, the conventional Stille reaction conditions are unacceptable for preparing some derivatives. Thus, modifications were made to the palladium-catalyzed cross-coupling, which enable such functionalities to be introduced in extremely mild conditions as well as in high yields. In all these coupling reactions, tris (dibenzylideneacetonyl)bis palladium(0) served as the catalyst while tri(2-furyl)phosphine exhibited its noticeable role in

enhancing the rate of activation of the ligand properties even at room temperature.

Suzuki Cross-Coupling Reaction:

The Stille coupling and the Suzuki coupling are very similar in many respects at a fundamental level; however, in terms of scalability for large scale production of the new compositions the Suzuki coupling has certain advantages. The necessary use of tin in stoichiometric amounts in the Stille reaction makes the Suzuki coupling more attractive. However, no generally applicable set of reaction conditions has yet been found to effect this reaction. At the same time, Suzuki coupling is an extremely useful approach for the incorporation of cyclopropyl, phenyl and certain other polyfluoroalkyl functionalities into a camptothecin scaffold. Recent reports by Wright and co-workers (Wright, S. W., 1994) simplified the reaction conditions by employing fluoride ion instead of incompatible bases to generate boronate anion. However, boronate anion may be crucial in the reaction medium to effect boron to palladium transmetallation. The recent report unambiguously suggested the capability of fluoride ions to exhibit significant affinity for boron and considerable stability of fluoborate ions. Additionally, the report also has addressed the favoring weak basicity and poor nucleophilicity of fluoride ions and the weakness of the palladium-fluorine bond in Suzuki coupling reactions.

Pyridone Chemistry

Effective functionalization of the pyridone moiety generated with in the camptothecin scaffold is effectively translated to prepare C-7 substituted camptothecin derivatives as highly lipophilic camptothecin analogs. The camptothecinone is thus utilized as a versatile synthon for preparing the key C-7 triflyloxy derivative. Regiospecificity at the γ position

is easily accomplished in the case of camptothecin series as the α position is already a part of the ring structure. The in situ generated trimethylsulfonyl enolate is conveniently hydrolyzed into the desired keto moiety in presence of water. This C-7-oxo-dihydro-CPT ("keto") intermediate upon treatment with dimethylsulfate and potassium carbonate yielded the 7-methoxycamptothecin. The keto compound is converted to respective 7-triflate by treating with triflic anhydride in the presence of a suitable organic base under anhydrous reaction conditions.

7-Trifluoromethanesulfonyloxy-20-O-acetylcamptothecin as an important intermediate

As a preferred embodiment of the present invention, a broad utility of C-7 camptothecin triflate is described in order to incorporate novel entities such as cross-coupled carbon-bearing moieties, vinyl substituents, acetylenic substituents, thioethers of pharmacological significance and also as a precursor for organocuprate addition at the C-7 position, permitting the incorporation of significantly bulky substituents such as trimethylsilyl.

C-7 Silylation

An efficient alkali metal-, such as lithium- or potassium- assisted alkylation or heteroatom incorporation strategy or organometallic-mediated alkylation or heteroatom incorporation on camptothecin has not yet been successfully accomplished due to the extreme sensitiveness of C-5 benzylic protons and the E-ring methylene protons associated with the lactone moiety. Conventional alkylation procedures suffer from the severe disadvantages that at least these two acidic sites of the molecule would be attacked by equivalents of the base. In view of these aspects, a persistent effort to circumvent these problems has been made. Several

palladium-mediated cross-coupling reactions were attempted with no success. The failure to provide the desired product via an organopalladium intermediate suggested the steric hindrance of the significantly bulkier trimethylsilyl group at C-7. In addition, several Minisci type reactions generated in situ free radical alkylation at the electron- deficient C-7 position. During our investigative efforts, we invented the following highly efficient methodology.

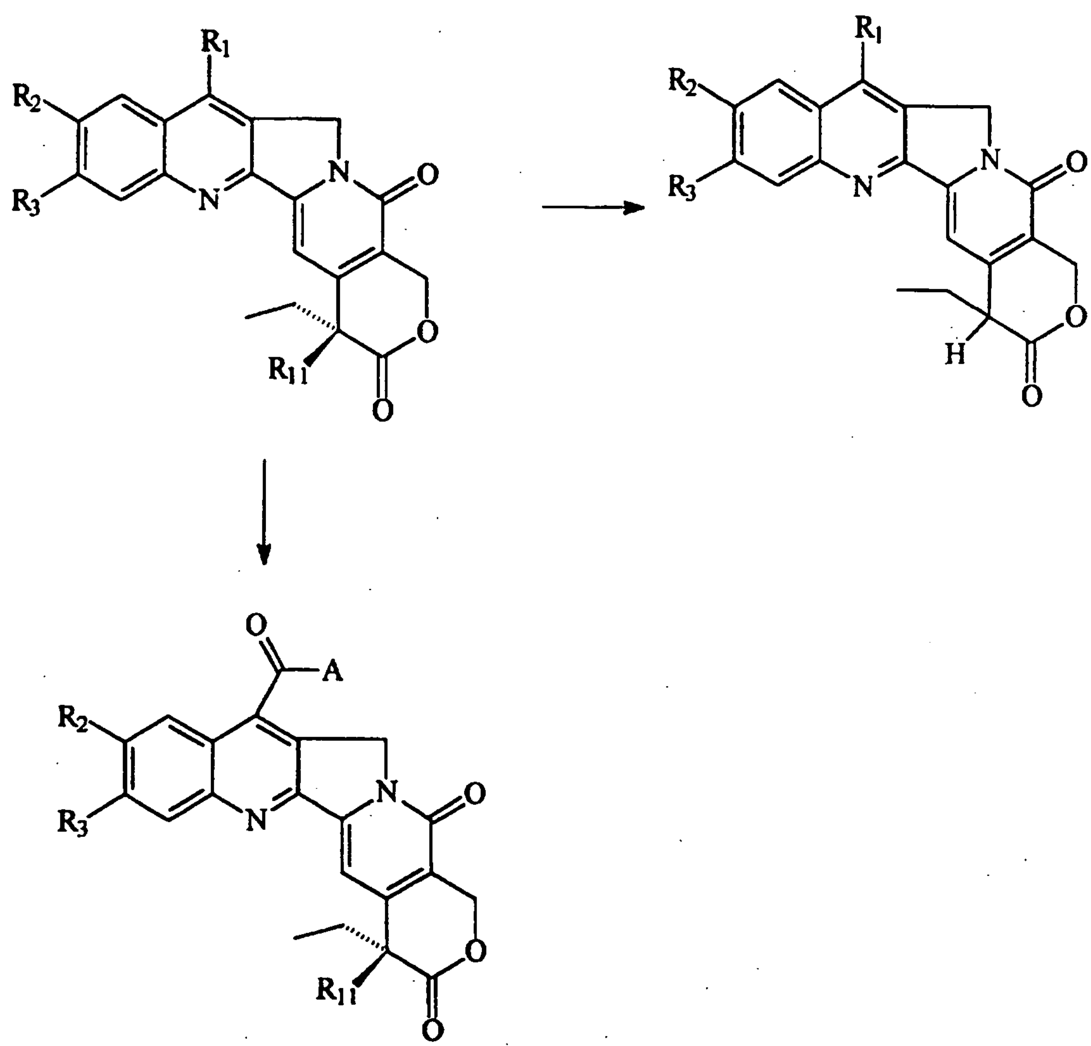
As a preferred embodiment of this invention, we provide an elegant organocuprate-mediated displacement of a C-7 triflate moiety with a trimethylsilyl group. The organocopper conjugate, analogous to Noyori's method, derived from cuprous iodide, n-butyl phosphine and trimethylsilyl lithium illustrated its versatility to displace the C-7 triflate preferentially without interfering with the C-5 benzylic protons or C-17 methylene protons at low temperature. The trimethylsilyl anion is conveniently generated from hexamethyldisilane in the presence of a suitable organic base at low temperature.

On the other hand, incorporation of the (trimethylsilyl)ethyl group at C-7 is accomplished <u>via</u> Minisci type alkylation. The key silyl synthon is prepared from (trimethylsilyl)propanol. The alcohol is oxidized into corresponding aldehyde using pyridinium chlorochromate in methylene chloride at room temperature. The aldehyde thus obtained is then fractionated to remove the self-condensed aldol products. The Minisci type alkylation is performed on camptothecin, whereby the overall synthetic approach could be reduced to a single step process.

The following Schemes illustrate the general processes used to produce novel camptothecin derivatives

of this invention, and in no way are to be considered limiting of the invention.

Scheme I



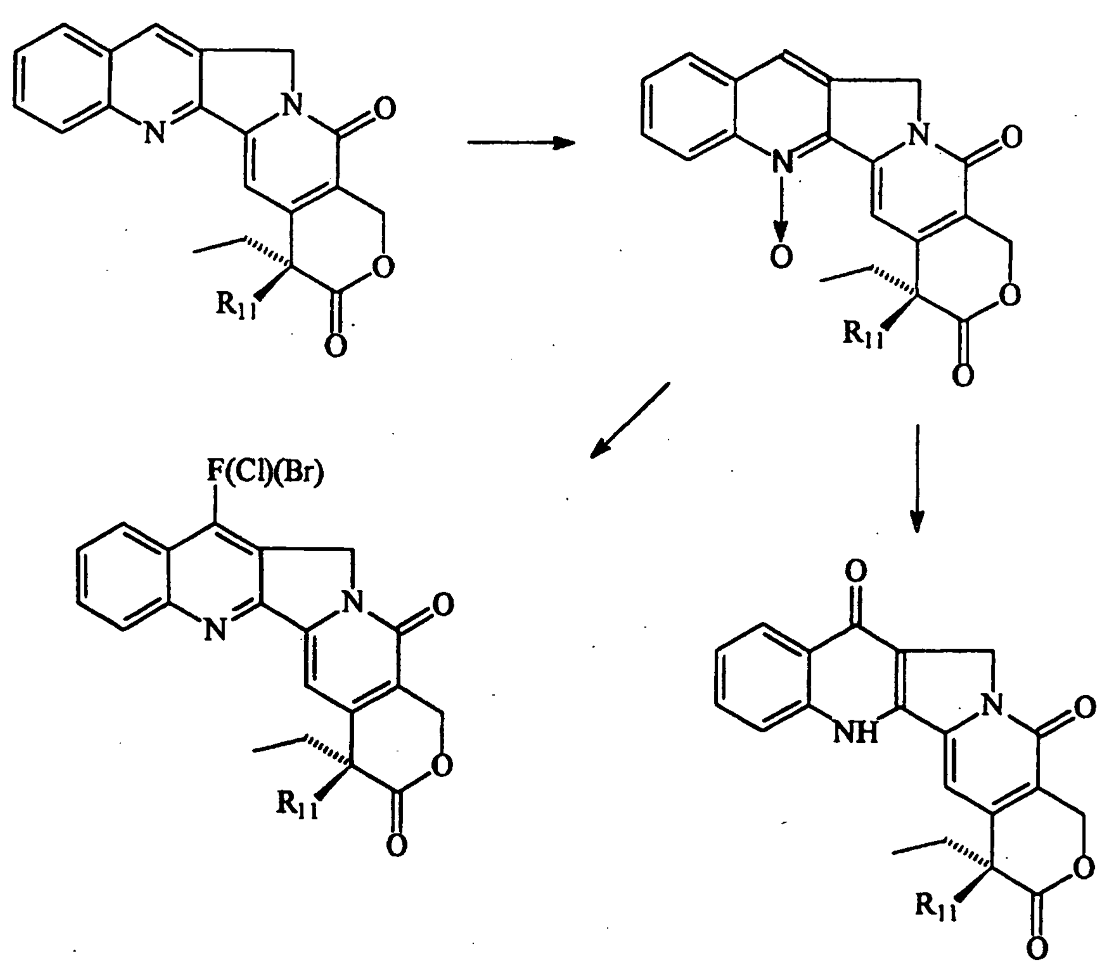
Scheme I illustrates the preparation of the C7-acyl derivatives of this invention, and also the preparation of the 20-deoxy derivative of CPT.

The selective acylation at the C7-position on the B-ring is achieved by the procedures outlined above. In the above scheme, "A" represents an alkyl chain of 1-6

carbon atoms, most preferably 1-2 carbon atoms, to form 7-acetyl-CPT or 7-propionyl-CPT, and R_{11} is hydroxy.

Conversion of the 20-hydroxy moiety to a hydrogen atom is achieved by a selective C-20 dehydroxylation. The novel dehydroxylation is accomplished by employing the versatility of Lawsson's Reagent or more gently by converting the 20-hydroxyl moiety into a better leaving group, preferably a trimethanesulfonyloxy block, followed by reductive cleavage using a respective stannyl hydride.

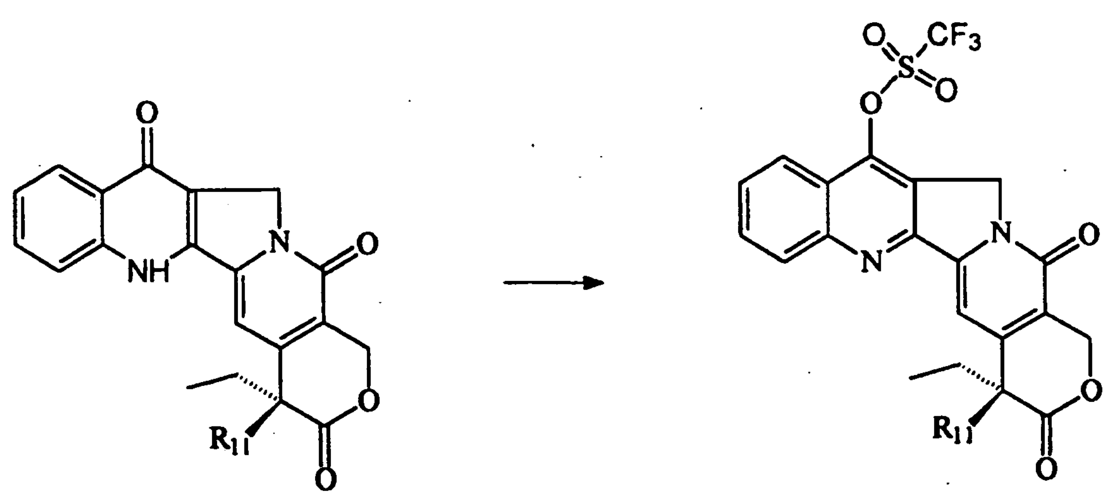
<u>Scheme II</u>



Scheme II illustrates the preparation of 7-halo CPT, and also the preparation of the key intermediate 7-keto CPT. The first step in the synthesis of either of these compounds is the conversion of CPT to camptothecin-1-oxide. In Scheme II, R_{11} is typically a protected hydroxy moiety, e.g. an aliphatic ether or acyloxy moiety, most preferably an acetoxy moiety, which is converted to hydroxy after the 7-position moieties have been added. The hydroxy group is thus protected from reaction with the halogenating agent. Typical deprotection of the 20-O-acetyl moiety and conversion to 20-hydroxy is accomplished by use of alkali metal salts and alcohols, most preferably potassium carbonate and methanol.

The halogenation at C-7 is achieved by the general procedures described above. Conversion and regioselectivity of CPT-1-oxide to 7-oxo-dihydro-CPT (7-keto CPT) is also described above, with the most preferred procedures outlined in Example 3 below. 7-Keto CPT is used extensively as a key intermediate in many of the selective schemes for producing the 7-substituted CPT derivatives of this invention. Schemes III and IV detail the synthetic procedures for making the novel CPT derivatives of this invention.

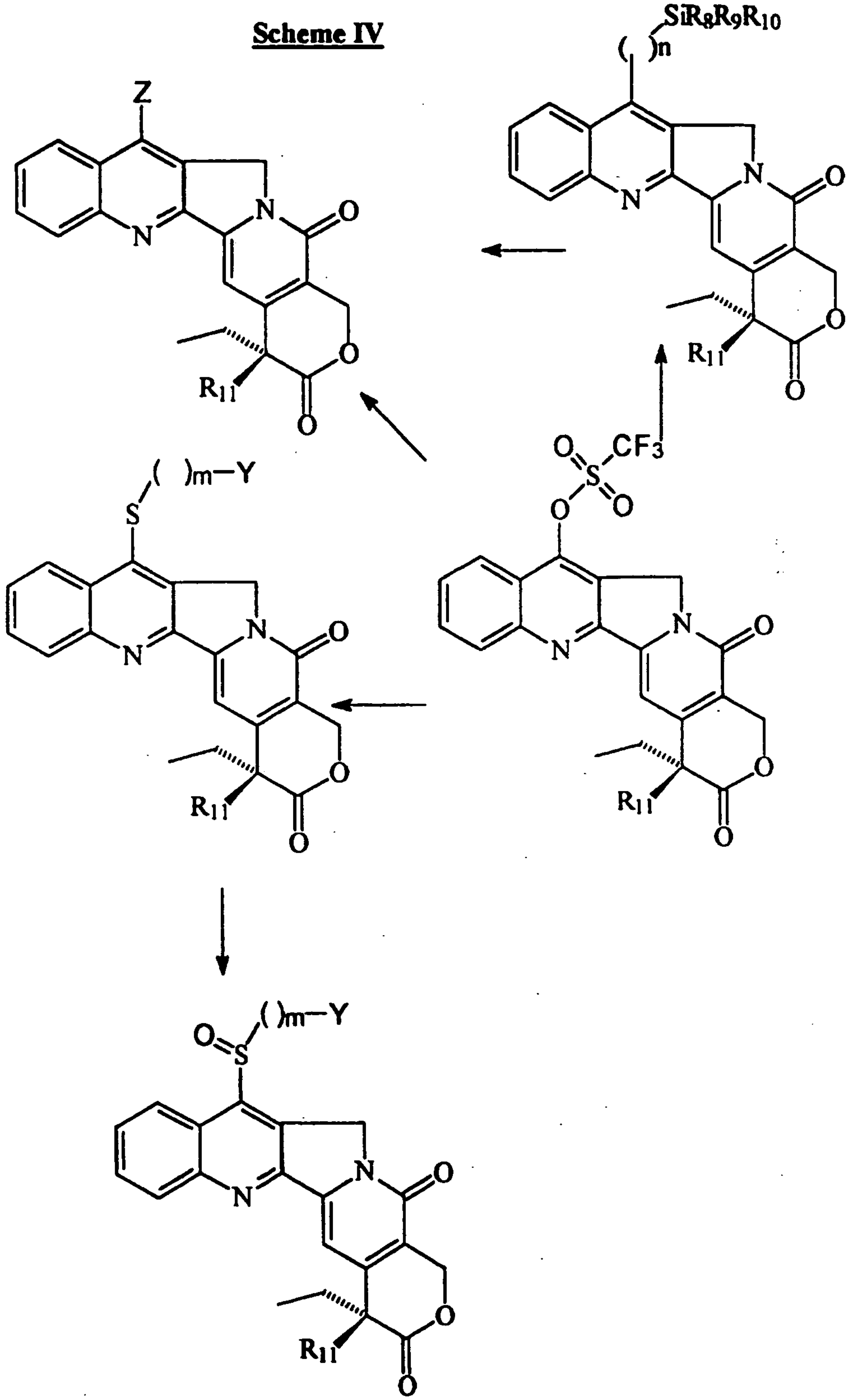
Scheme III



Scheme III illustrates the synthesis of the 7-trifluoromethanesulfonyloxy intermediate which is key to the substitution of the various 7-position moieties which form the subject matter of this invention.

As shown, 7-keto CPT, after protection of the hydroxy group as described above in connection with Scheme II but in this instance against triflylation, is converted into the 7-triflate intermediate by reacting with a sulfate ester and an alkali metal salt, then with triflic anhydride (hexafluorodimethylsulfonyl ether). The resulting 7-triflate intermediate possesses excellent properties for substitution reactions to be performed on the molecule, allowing for diverse moieties to be attached to the CPT scaffold.

<u>**Scheme IV**</u>


Z
N
N
O
O
O
R11
SiR8R9R10
( )n
N
N
O
O
O
R11
S
( )m—Y
N
N
O
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O
R11
O
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CF3
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S
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R11

Scheme IV illustrates the synthesis of the novel C7-substituted CPT derivatives of this invention. The key intermediate, 7-trifluoromethanesulfonyloxy CPT, is converted into one of the novel compounds of this invention by following the general methods outlined in the specification, supra.

The two general moieties which are substituted directly for the triflyloxy moiety are the silyl moieties and the thioether moieties shown in scheme IV. As stated above, the silyl moieties are formed through a modified Stille coupling, through the use of a palladium mediated tributyltin-alkylsilane substitution. The $(\ )_n$- refers to an alkyl (or alkenyl or alkynyl) group, where n stands for the number of carbon atoms, preferably 0 to 6, most preferably 0 to 3. When n is 0, the preferred synthesis utilizes an organolithium-mediated displacement using hexamethyl disilane as the preferred reagent.

The silyl moieties may be converted into 7-alkenyl or 7-alkynyl moieties (designated by the letter "Z"), by reacting with an alkali metal salt, which both removes the silyl moiety and also serves to convert the 20-O-acetyl moiety to hydroxy. 7-alkenyl and 7-alkynyl substituted CPT derivatives may also be prepared directly from the 7-triflate by the modified Stille coupling as described above.

7-thioethers are prepared by reacting the 7-triflate with the appropriate alkyl sulfide under basic conditions. In the scheme shown $(\ )_m$- stands for an alkyl (or alkenyl or alkynyl) group and m is 0 to 6, preferably 1 to 3. Y is an optional silyl moiety, such as trimethylsilyl, which may optionally be appended to the terminal end of the reagent, and will be transferred to the resulting compound. An example of such a thioether reagent is 1-trimethylsilyl-2-mercaptoethane, which would form 7-(β-trimethylsilyl)ethylthio-CPT.

7-thioethers may be converted into the 7-sulfinyl derivatives by reacting with a peracid, such as a perbenzoic acid, most preferably m-chloroperbenzoic acid. Other derivatives may be prepared by utilizing the syntheses described above, in conjunction with the specific examples listed below.

Specific Examples

The following non-limiting examples illustrate the invention. "Florisil" is a Registered Trade Mark.

EXAMPLE 1

7-Acetylcamptothecin

Camptothecin (5 g, 14.36 mmols) was dissolved in trifluoroacetic acid: acetic acid (60 mL; ratio, 1:1) and added deionized water (15 mL) and freshly distilled acetaldehyde (20 mL; excess) followed by dropwise addition of concentrated sulfuric acid (5 mL) at 0°C using an ice bath over a period of 15 min. To the above stirred reaction medium is then introduced 70% aqueous solution of t-butylhydroperoxide (3 mL) followed by iron sulfate heptahydrate (7.8 g, 28 mmol) in 1 mL water. The reaction mixture was then stirred at 0° C to 25° C for an additional 24 hours. The reaction mixture was then diluted with water and extracted with diethyl ether (500 mL X 1), chloroform (250 mL X 1) and then using n-butanol (250 mL X 4). The organic portions were extracted using diethyl ether and chloroform and discarded as fractions lacking desired product, while the n-butanol portion was concentrated to dryness at 40° C and the crude product was recrystallized from a 90% chloroform-methanol mixture to furnish 4.2 g of the title compound (75% yield).

^{1}H NMR (300 MHz; d6-DMSO): 0.87 δ (3H, t, J= 7Hz); 1.86 δ (2H, q, J= 5 Hz); 2.78 δ (3H, s); 5.29 δ (2H, m); 5.38 δ (2H, m); 6.51 δ (1H, bs, OH); 7.35 δ (2H, s); 7.78 δ (1H,

t, J= 13.5 Hz); 7.92 δ (1H, t, J= 7.64 Hz); 8.13 δ (1H, d, J= 8.35 Hz); 8.23 d (1H,d, J= 8.38 Hz)

^{13}C NMR: δ 7.84, 30.41, 31.7, 50.27, 65.35, 73.21, 97.42, 119.78, 123.26, 124.86, 126.12, 131. 4, 138.5, 143.87, 143.25, 145.31, 149.34, 150.05, 156.63, 157.68, 172.46, 205.05

FAB-MS: 391 (M+1)

EXAMPLE 2

7-Propionylcamptothecin

Camptothecin (1 g, 2.8 mmols) was dissolved in trifluoroacetic acid-acetic acid (6 mL; ratio, 1:1) and deionized water (3 mL) and freshly distilled propionaldehyde (3.0 mL; excess) were added, followed by dropwise addition of concentrated sulfuric acid (1 mL) at 0° C using an ice bath during 15 min. To the above stirred reaction medium was then introduced a 70% aqueous solution of t-butylhydroperoxide (3 mL), followed by iron sulfate heptahydrate (1.56 g, 5.6 mmol) in 1 mL water. The reaction mixture was then stirred at 0° C to 25° C for an additional 24 hours. The reaction mixture was then diluted with water and extracted with diethyl ether (100 mL X 1), chloroform (50 mL X 1) and then using n-butanol (100 mL X 4). The organic portions extracted out using diethyl ether and chloroform were discarded as fractions lacking desired product, while the n-butanol portion was concentrated to dryness at 40° C and the crude product was recrystallized from a 90% chloroform-methanol mixture to furnish 0.86 g of the title compound (74% yield).

^{1}H NMR (300 MHz; d6-DMSO): 0.87 δ (3H, t, J= 7 Hz); 1.26 δ (3H, t, J= 6.8 Hz); 1.84 δ (2H, q, J= 5 Hz); 3.15 δ (2H, q, J= 5.1 Hz); 5.29 δ (2H, m); 5.38 δ (2H, m); 6.51 δ (1H, bs); 7.35 δ (2H, s); 7.72 δ (1H, t, J= 13.5 Hz); 7.90 δ (1H, t, J= 7.64 Hz); 7.98 δ (1H, d, J= 8.35 Hz); 8.20 δ (1H,d, J= 8.38 Hz)

^{13}C NMR: δ 7.54, 7.74, 30.31, 36.7, 49.81, 65.21, 72.33, 96.88, 119.48, 123.12, 125.69, 130.63, 131.72, 140.97, 143.14, 143.25, 145.31, 149.97, 156.55, 157.68, 172.36, 204.91

FAB-MS: 405 (M+1)

EXAMPLE 3

7-oxo-dihydrocamptothecin (also termed 7-ketocamptothecin or camptothecinone)

Camptothecin 1-oxide (1 g, 2.7 mmol) was dissolved in trifluoroacetic acid (2 mL) and anhydrous methylene chloride (15 mL) and trifluoroacetic anhydride (16 mL) was added. The reaction mixture was then refluxed under a positive pressure of argon for 48 hours. The reaction mixture was then cooled to room temperature and diluted with water (15 mL) and stirred for 6 hours. The product was then precipitated out by pouring the reaction mixture into crushed ice. The precipitated product was then filtered, washed with excess water, once with diethyl ether and dried under vacuum to obtain 687 mg of the desired product (66% yield).

^{1}H NMR (300 MHz; d6-DMSO): 0.87 δ (3H, t, J= 7Hz); 1.96 δ (2H, q, J= 5 Hz); 2.78 δ (3H, s); 5.86 δ (2H, m); 5.40 δ (2H, m); 6.81 δ (1H, bs); 7.38 δ (1H, t, J= 13.5 Hz); 7.47 δ (2H, s); 7.71 δ (1H, t, J= 7.64 Hz); 7.73 δ (1H, d, J= 8.35 Hz); 8.14 δ (1H,d, J= 8.38 Hz)

^{13}C NMR: δ 6.89, 29.55, 49.6, 66.123, 79.90, 94.78, 105.12, 118.48, 123.31, 124.26, 124.95, 132.06, 141.69, 143.55, 155.35, 164.88, 200.432

FAB-MS: 461 (M+1 for the triflic acid salt)

EXAMPLE 4

7-Trifluoromethanesulfonyloxy-20-O-acetylcamptothecin

20-O-acetylcamptothecinone (220 mg, 0.54 mmols) was dissolved in anhydrous pyridine (4 mL) and anhydrous methylene chloride (10 mL). The above solution was

stirred well while lowering the temperature to -10° C using an ice bath. To it was then slowly introduced triflic anhydride (0.5 mL, 1.05 mol) and the reaction continued to completion. The reaction mixture was then diluted with methylene chloride (20 mL), water-washed and the organic portion was concentrated to dryness. The product thus obtained upon analysis was found substantially pure for the subsequent step.

^{1}H NMR (300 MHz; $CDCl_3$): 0.87 δ (3H, t, J= 5.4 Hz); 2.12 δ (2H, q, J= 7.2 Hz); 2.21 δ (3H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.49 δ (2H, q, J= 2.5 Hz); 7.14 δ (1H, s); 7.97 δ (1H, t, J= 7.2 Hz); 8.05 δ (1H, t, J= 7.9 Hz); 8.12 δ (1H, d, J= 8.4 Hz); 8.35 δ (1H, d, J= 6.2 Hz)
FAB-MS: 540 (M+1)

EXAMPLE 5

20-O-acetyl-7-chlorocamptothecin

20-O-acetylcamptothecin-1-oxide (800 mg, 1.96 mmols) was taken up as a suspension in phosphorus oxychloride (10 mL) and stirred at 40° C for 48 hours under a positive blanket of inert gas. The reaction mixture was then diluted with methylene chloride (25 mL) and cooled down to 0° C using an ice bath. The reaction mixture was then diluted with water (50 mL) and stirred for 3 hours. The organic portion was then extracted out using methylene chloride (50 mL X 5), concentrated and flashed through a bed of silica gel using chloroform to obtain the desired product (642 mg; 77.1%)

^{1}H NMR (300 MHz; $CDCl_3$): 0.90 δ (3H, t, J= 5.4 Hz); 2.12 δ (2H, q, J= 7.2 Hz); 2.21 δ (3H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.49 δ (2H, q, J= 2.5 Hz); 7.07 δ (1H, s); 7.87 δ (1H, t, J= 7.2 Hz); 7.95 δ (1H, t, J= 7.9 Hz); 8.21 δ (1H, d, J= 8.4 Hz); 8.27 δ (1H, d, J= 6.2 Hz)
FAB-MS: 425.1 (M+1)

EXAMPLE 6

7-Chlorocamptothecin

20-O-acetyl-7-chlorocamptothecin (100 mg, 0.23 mmols) was dissolved in reagent grade methanol (20 mL) and aqueous potassium carbonate (20 mg in 5 mL water) was added and the mixture stirred for 1 hour at room temperature. The resulting reaction mixture was concentrated to 5 mL under vacuum and diluted with water (20 mL). The precipitated product was then filtered, dried and analyzed to the desired product (60 mg; 67 %).

^{1}H NMR (300 MHz; $CDCl_3$): 0.87 δ (3H, t, J= 5.4 Hz); 1.85 δ (2H, q, J= 7.2 Hz); 3.6 δ (1H, s); 5.31 δ (2H, s); 5.43 δ (2H, s); 7.07 δ (1H, s); 7.87 δ (1H, t, J= 7.2 Hz); 7.95 δ (1H, t, J= 7.9 Hz); 8.21 δ (1H, d, J= 8.4 Hz); 8.27 δ (1H, d, J= 6.2 Hz)

^{13}C NMR: δ 7.54, 30.31, 49.81, 65.21, 72.33, 96.88, 119.48, 123.12, 125.69, 126.96,130.63, 131.72, 140.97, 143.14, 143.25, 145.31, 149.97, 156.55, 157.68, 172.36

FAB-MS: 383.1 (M+1)

EXAMPLE 7

20-O-acetyl-7-vinylcamptothecin

The 20-O-acetyl-7-triflate (100 mg, 0.1855 mmol) was dissolved in anhydrous and degassed anhydrous dimethylformamide (5 mL) and zinc chloride (50.5 mg, 0.371 mmol) added. To it was then added tris(dibenzylideneacetonyl)bis palladium(0) (17 mg, 0.371 mmol) followed by tri(2-furyl)phosphine (20 mg, 0.074 mmol). The resulting solution was stirred for approximately 30 minutes at room temperature. Then vinyl tributyltin (60 mL, 0.223 mmol) was added. The reaction mixture was then stirred at room temperature for 48 hours. The resulting dark brown colored reaction mixture was then diluted with methylene chloride (25 mL), filtered, washed with water (15 mL). The crude product

obtained after concentration was then flashed through a columnar bed of activated magnesium silicate "Florisil", the fractions pooled, concentrated, dried under vacuum and analyzed.

^{1}H NMR (300 MHz; $CDCl_3$): 0.87 δ (3H, t, J= 5.4 Hz); 1.85 δ (2H, q, J= 7.2 Hz); 2.31 δ (3H, s); 3.6 δ (1H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, s); 6.15 δ (2H, dd, J= 12.8 Hz); 6.4 δ (1H, d, J= 2.5 Hz); 7.07 δ (1H, s); 7.87 δ (1H, t, J= 7.2 Hz); 7.95 δ (1H, t, J= 7.9 Hz); 8.21 δ (1H, d, J= 8.4 Hz); 8.27 δ (1H, d, J= 6.2 Hz)

EXAMPLE 8

7-Vinylcamptothecin

20-O-acetyl-7-vinylcamptothecin (100 mg, 0.23 mmols) was dissolved in reagent grade methanol (20 mL) and aqueous potassium carbonate (20 mg in 5 mL water) added and the mixture stirred for 2 hours at low temperature. The resulting reaction mixture was acidified to pH 4 using 1N HCl and the precipitated product was filtered, dried and analyzed to the desired product (30 mg; 47%).

^{1}H NMR (300 MHz; $CDCl_3$): 0.87 δ (3H, t, J= 5.4 Hz); 1.85 δ (2H, q, J= 7.2 Hz); 3.6 δ (1H, s); 3.6 δ (1H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, m); 6.15 δ (2H, dd, J= 12.8 Hz); 6.4 δ (1H, d, J= 2.5 Hz); 7.07 δ (1H, s); 7.87 δ (1H, t, J= 7.2 Hz); 7.95 δ (1H, t, J= 7.9 Hz ; 8.21 δ (1H, d, J= 8.4 Hz); 8.27 δ (1H, d, J= 6.2 Hz)

^{13}C NMR: δ 7.54, 30.31, 49.81, 65.21, 72.33, 96.88, 99.6, 119.48, 123.12, 125.69, 126.96,130.63, 131.72, 137.2, 140.97, 143.14, 143.25, 145.31, 149.97, 156.55, 157.68, 172.36

FAB-MS: 373(M+1)

EXAMPLE 9

20-O-acetyl-7-[(γ-trimethylsilyl)propyn-2-yl]camptothecin

The 20-O-acetyl-7-triflate (100 mg, 0.1855 mmol) was dissolved in anhydrous and degassed anhydrous dimethylformamide (5 mL) and zinc chloride (50.5 mg, 0.371 mmol) added. To it was then added tris(dibenzylideneacetonyl)bis palladium(0) (17 mg, 0.371 mmol), diisopropyl ethylamine (50 μL), followed by tri(2-furyl)phosphine (20 mg, 0.074 mmol). The resulting solution was stirred for approximately 30 minutes at room temperature. Then propargylic trimethylsilane (prop-2-ynyl trimethylsilane) (0.1 mL) was added. The reaction mixture was then stirred at room temperature for 48 hours. The resulting dark brown colored reaction mixture was then diluted with methylene chloride (25 mL), filtered, washed with water (15 mL). The crude product obtained after concentration was then flashed through a columnar bed of "Florisil", the fractions pooled, concentrated, dried under vacuum and analyzed.

^1H NMR (300 MHz; $CDCl_3$): 0.38 δ (9H,s); 0.87 δ (3H, t, J= 5.4 Hz); 2.3 δ (2H, q, J= 7.2 Hz); 2.31 δ (3H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, m); 7.07 δ (1H, s); 7.87 δ (1H, t, J= 7.2 Hz); 7.95 δ (1H, t, J= 7.9 Hz); 8.21 δ (1H, d, J= 8.4 Hz); 8.27 δ (1H, d, J= 6.2 Hz)

EXAMPLE 10

20-O-acetyl-7-(methylthio)camptothecin

The intermediate triflate (100 mg, 0.186 mmol) was dissolved in anhydrous 1,4-dioxane and cooled to 0° C under a stream of argon. To it was then added diisopropyl ethylamine (0.1 mL; 0.557 mmole) and methanethiol slowly bubbled in for 5 minutes and then the reaction mixture was stirred under a balloon pressure for 15 hours. After 15 hours, the reaction mixture was diluted with methylene chloride (25 mL) and washed with water (20 mL X 4), dried over anhydrous sodium sulfate,

filtered and concentrated to obtain the crude product of the title compound in approximately 80.5% yield.

^{1}H NMR (300 MHz; $CDCl_3$): 0.87 δ (3H, t, J= 5.4 Hz); 2.31 δ (2H, q, J= 7.2 Hz); 2.28 δ (3H, s); 2.31 δ (3H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, m); 7.07 δ (1H, s); 7.65 δ (1H, t, J= 7.2 Hz); 7.75 δ (1H, t, J= 7.9 Hz); 8.1 δ (1H, d, J= 8.4 Hz); 8.61 d (1H, d, J= 6.2 Hz).

FAB-MS: 438 (M+1)

EXAMPLE 11

7-(Methylthio)camptothecin

20-O-acetyl-7-(methylthio)camptothecin (100 mg, 0.23 mmols) was dissolved in reagent grade methanol (20 mL) and aqueous potassium carbonate (25 mg in 0.1 mL water) added and the mixture stirred for about 3 hours at low temperature. The resulting reaction mixture was acidified with 1N HCl to precipitate the lactone form of the compound. The precipitated product was then filtered, washed with water (10 mL X 4) and with ether (10 mL), dried under vacuum. The pale yellow powder was then analyzed to the desired product (65 mg; 77%).

^{1}H NMR (300 MHz; $CDCl_3$): 0.87 δ (3H, t, J= 5.4 Hz); 2.28 δ (2H, q, J= 7.2 Hz); 2.31 δ (3H, s); 3.6 δ (1H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, s); 7.07 δ (1H, s); 7.65 δ (1H, t, J= 7.2 Hz); 7.75 δ (1H, t, J= 7.9 Hz); 8.1 δ (1H, d, J= 8.4 Hz); 8.61 δ (1H, d, J= 6.2 Hz)

FAB-MS: 394 (M+1)

EXAMPLE 12

20-O-acetyl-7-(methylsulfinyl)camptothecin

20- Acetoxy-7-(methylthio)camptothecin (25 mg, 0.057 mmol) was dissolved in anhydrous methylene chloride (10 mL) and cooled to 0° C using an ice bath under a stream of argon. Then freshly purified m-chloroperbenzoic acid (10.3 mg, 1 equivalent) was added and the reaction

mixture stirred for 2 hours at low temperature. The reaction mixture was then diluted with methylene chloride (20 mL) and washed with water (10 mL X 4), dried and concentrated to obtain the title compound in the crude form. The product was then flash chromatographed over a bed of "Florisil" using 10% methanol in chloroform to furnish the desired sulfoxide as a diastereomeric mixture in 60% yield.

^{1}H NMR (300 MHz; $CDCl_3$): 0.87 δ (3H, t, J= 5.4 Hz); 2.29 δ (2H, q, J= 7.2 Hz); 2.31 δ (3H, s); 3.32 δ (3H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, m); 7.07 δ (1H, s); 7.65 δ (1H, t, J= 7.2 Hz); 7.75 δ (1H, t, J= 7.9 Hz); 8.1 δ (1H, d, J= 8.4 Hz); 8.61 δ (1H, d, J= 6.2 Hz)
FAB-MS: 454 (M+1)

EXAMPLE 13

7-(Methylsulfinyl)camptothecin

20-O-acetyl-7-(methylsulfinyl)camptothecin (100 mg, 0.18 mmols) was dissolved in reagent grade methanol (20 mL) and aqueous potassium carbonate (25 mg in 0.1 mL water) added and the mixture stirred for about 3 hours at low temperature. The resulting reaction mixture was acidified with 1N HCl to precipitate the lactone form of the compound. The precipitated product was then filtered, washed with water (10 mL X 4) and with ether (10 mL), and dried under vacuum. The pale yellow powder was then analyzed to the desired product (65 mg; 61%).

^{1}H NMR (300 MHz; $CDCl_3$): 0.87 δ (3H, t, J= 5.4 Hz); 2.21 δ (2H, q, J= 7.2 Hz); 3.6 δ (1H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, m); 7.07 δ (1H, s); 7.65 δ (1H, t, J= 7.2 Hz); 7.75 δ (1H, t, J= 7.9 Hz); 8.1 δ (1H, d, J= 8.4 Hz); 8.61 δ (1H, d, J= 6.2 Hz)
FAB-MS: 411 (M+1)

EXAMPLE 14

20-O-acetyl-7-(ethylthio)camptothecin

The intermediate triflate (100 mg, 0.186 mmole) was dissolved in anhydrous 1,4-dioxane and cooled to 0° C under a stream of argon. To it was then added diisopropyl ethylamine (0.1 mL; 0.557 mmole) and ethanethiol (0.4ml) slowly added. The reaction mixture was then stirred under a balloon pressure for 15 hours in a well ventilated hood. After 15 hours, the reaction mixture was diluted with methylene chloride (25 mL) and washed with water (20 mL X 4), dried over anhydrous sodium sulfate, filtered and concentrated to obtain the crude product of the title compound in approximately 80.5% yield.

^{1}H NMR (300 MHz; $CDCl_3$): 0.87 δ (3H, t, J= 5.4 Hz); 1.26 δ (3H, t, J= 5.8 Hz); 2.21 δ (2H, q, J= 7.2 Hz); 2.31 δ (3H, s); 2.28 δ (3H, s); 3.19 δ (2H, q, J= 7.2 Hz); 3.6 δ (1H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, m); 7.07d (1H, s); 7.65 δ (1H, t, J= 7.2 Hz); 7.75 δ (1H, t, J= 7.9 Hz); 8.1 δ (1H, d, J= 8.4 Hz); 8.58 δ (1H, d, J= 6.2 Hz)

FAB-MS: 468 (M+1)

EXAMPLE 15

7-(Ethylthio)camptothecin

20-O-acetyl-7-(ethylthio)camptothecin (100 mg, 0.21 mmole) was dissolved in reagent grade methanol (20 mL) and aqueous potassium carbonate (25 mg in 0.1 mL water) added and the mixture stirred for about 3 hours at low temperature. The resulting reaction mixture was acidified with 1N HCl to precipitate the lactone form of the compound. The precipitated product was then filtered, washed with water (10 mL X 4) and with ether (10 mL), dried under vacuum. The pale yellow powder was then analyzed to the desired product (69 mg; 76%).

^{1}H NMR (300 MHz; $CDCl_3$): 0.87 δ (3H, t, J= 5.4 Hz); 1.26 δ (3H, t, J= 5.8 Hz); 2.21 δ (2H, q, J= 7.2 Hz); 2.28 δ (3H, s); 3.19 d (2H, q, J= 7.2 Hz); 3.6 d (1H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, m); 7.07 δ (1H, s); 7.65 δ (1H, t, J= 7.2 Hz); 7.75 δ (1H, t, J= 7.9 Hz); 8.1 δ (1H, d, J= 8.4 Hz); 8.58 δ (1H, d, J= 6.2 Hz)

FAB-MS: 425 (M+1)

EXAMPLE 16

20-O-acetyl-7-(isopropylthio)camptothecin

The intermediate triflate (100 mg, 0.186 mmol) was dissolved in anhydrous 1, 4- dioxane and cooled to 0 °C under a stream of argon. To it was then added diisopropyl ethylamine (0.1 mL; 0.557 mmole) and isopropanethiol (1mL) slowly added and then the reaction mixture was stirred under a balloon pressure for 15 hours in a well ventilated hood. After 48 hours, the reaction mixture was diluted with methylene chloride (25 mL) and washed with water (20 mL X 4), dried over anhydrous sodium sulfate, filtered and concentrated to obtain the crude product of the title compound in approximately 60.5% yield.

^{1}H NMR (300 MHz; $CDCl_3$): 0.87 δ (3H, t, J= 5.4 Hz); 1.26 δ (6H, d, J= 5.8 Hz); 2.19 δ (2H, q, J= 7.2 Hz); 2.31 δ (3H, s); 2.28d (3H, s); 3.59 δ (2H, q, J= 7.2 Hz); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, m); 7.07 δ (1H, s); 7.65 δ (1H, t, J= 7.2 Hz); 7.75 δ (1H, t, J= 7.9 Hz); 8.1 δ (1H, d, J= 8.4 Hz); 8.58 δ (1H, d, J= 6.2 Hz)

FAB-MS: 482 (M+1)

EXAMPLE 17

20-O-acetyl-7-(phenylthio)camptothecin

The intermediate triflate (100 mg, 0.186 mmol) was dissolved in anhydrous 1,4-dioxane and cooled to 0° C

under a stream of argon. To it was then added diisopropyl ethylamine (0.1 mL; 0.557 mmole) and phenyl mercaptan (0.2 mL) was slowly added and the reaction mixture then stirred under a balloon pressure for 15 hours in a well ventilated hood. After 48 hours, the reaction mixture was diluted with methylene chloride (25 mL) and washed with water (20 mL X 4), dried over anhydrous sodium sulfate, filtered and concentrated to obtain the crude product of the title compound in approximately 80.5% yield.

^{1}H NMR (300 MHz; $CDCl_3$): 0.87 δ (3H, t, J= 5.4 Hz); 2.19 δ (2H, q, J= 7.2 Hz); 2.28 δ (3H, s); 4.82 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, s); 6.93 - 7.61 δ (5H, m); 7.07 δ (1H, s); 7.65 δ (1H, t, J= 7.2 Hz); 7.75 δ (1H, t, J= 7.9 Hz); 8.1 δ (1H, d, J= 8.4 Hz); 8.61 δ (1H, d, J= 6.2 Hz)

^{13}C NMR: δ 7.32, 20.56, 31.63, 50.08, 66.91, 66.98, 75.43, 95.97, 120.47, 125.46, 127.14, 127.49, 128.5, 128.55, 128.72, 129.07, 129.92, 130.15, 130.99, 131.12, 131.56, EXAMPLE 18140.19, 145.76, 146.11, 149.23, 152.03, 157.07, 167.59, and 169.94

FAB-MS (M+1): 500

<u>7-(Phenylthio)camptothecin</u>

20-O-acetyl-7-(phenylthio)camptothecin (100 mg, 0.21 mmols) was dissolved in reagent grade methanol (20 mL) and aqueous potassium carbonate (25 mg in 0.1 mL water) added and the mixture stirred for about 3 hours at low temperature. The resulting reaction mixture was acidified with 1N HCl to precipitate the lactone form of the compound. The precipitated product was then filtered, washed with water (10 mL X 4) and with ether (10 mL), dried under vacuum. The pale yellow powder was then analyzed to the desired product (79 mg; 80 %).

^1H NMR (300 MHz; $CDCl_3$): 0.87 δ (3H, t, J= 5.4 Hz); 1.89 δ (2H, q, J= 7.2 Hz); 3.6 δ (1H, s); 4.82 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, s); 6.93 - 7.61 δ (5H, m); 7.07 δ (1H, s); 7.65 δ (1H, t, J= 7.2 Hz); 7.75 δ (1H, t, J= 7.9 Hz); 8.1 δ (1H, d, J= 8.4 Hz); 8.61 δ (1H, d, J= 6.2 Hz)

^{13}C NMR: δ 7.32, 20.56, 31.63, 50.08, 66.91, 66.98, 75.43, 95.97, 120.47, 125.46, 127.14, 127.49, 128.5, 128.55, 128.72, 129.07, 129.92, 130.15, 130.99, 131.12, 131.56, 140.19, 145.76, 146.11, 149.23, 152.03, 157.07, 167.59, and 169.94

FAB-MS (M+1): 457

EXAMPLE 19

20-O-acetyl-7-[(4-fluorophenyl)thio]camptothecin

The intermediate triflate (100 mg, 0.186 mmol) was dissolved in anhydrous 1,4-dioxane and cooled to 0° C under a stream of argon. To it was then added diisopropyl ethylamine (0.1 mL; 0.557 mmole), 4-fluorophenylmercaptan (0.2 mL) was slowly added and the reaction mixture then stirred under a balloon pressure for 15 hours in a well ventilated hood. After 48 hours, the reaction mixture was diluted with methylene chloride (25 mL) and washed with water (20 mL X 4), dried over anhydrous sodium sulfate, filtered and concentrated to obtain the crude product of the title compound in approximately 80.5% yield.

^1H NMR (300 MHz; $CDCl_3$): 0.87 δ (3H, t, J= 5.4 Hz); 2.19 δ (2H, q, J= 7.2 Hz); 2.28 δ (3H, s); 4.82 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, m); 6.93 - 7.61 δ (4H, m); 7.07 δ (1H, s); 7.65 δ (1H, t, J= 7.2 Hz); 7.75 δ (1H, t, J= 7.9 Hz); 8.1 δ (1H, d, J= 8.4 Hz); 8.61 δ (1H, d, J= 6.2 Hz)

^{13}C NMR: δ 7.42, 31.63, 50.08, 66.01, 66.98, 72.49, 98.01, 116.92, 117.21, 118.84, 125.12, 128.38, 128.52, 130.43, 130.84, 131.48, 133.19, 133.3, 139.69, 146.17, 149.36, 149.36, 149.98, 152.07, 160.99 and 173.82

FAB-MS (M+1): 518

EXAMPLE 20

7-[(4-fluorophenyl)thio]camptothecin

20-O-acetyl-7-[(4-fluorophenyl)thio]camptothecin (100 mg, 0.21 mmols) was dissolved in reagent grade methanol (20 mL) and aqueous potassium carbonate (25 mg in 0.1 mL water) added and the mixture stirred for about 3 hours at low temperature. The resulting reaction mixture was acidified with 1N HCl to precipitate the lactone form of the compound. The precipitated product was then filtered, washed with water (10 mL X 4) and with ether (10 mL), dried under vacuum. The pale yellow powder was then analyzed to the desired product (79 mg; 80 %).

^{1}H NMR (300 MHz; $CDCl_3$): 0.87 δ (3H, t, J= 5.4 Hz); 2.23 δ (2H, q, J= 7.2 Hz); 3.6 δ (1H, s); 4.82 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, s); 6.93 - 7.61 δ (4H, m); 7.07 δ (1H, s); 7.65 δ (1H, t, J= 7.2 Hz); 7.75 δ (1H, t, J= 7.9 Hz); 8.1 δ (1H, d, J= 8.4 Hz); 8.61 δ (1H, d, J= 6.2 Hz)

^{13}C NMR: δ 7.42, 31.63, 50.08, 66.01, 66.98, 72.49, 98.01, 116.92, 117.21, 118.84, 125.12, 128.38, 128.52, 130.43, 130.84, 131.48, 133.19, 133.3, 139.69, 146.17, 149.36, 149.36, 149.98, 152.07, 160.99 and 173.82

FAB-MS (M+1): 475

EXAMPLE 21

20-O-acetyl-7-[trimethylsilyl]camptothecin

Hexamethyldisilane (62 μL, 0.3 mmol) was taken up in a flame-dried round bottom flask under argon and to it was added anhydrous hexamethyl phosphoramide (0.5 mL) and

anhydrous tetrahydrofuran at room temperature. The reaction medium was then cooled to 0°C using an ice bath and methyllithium (220 µL, estimated as 30.8 mg per mL) introduced. The dark colored solution was then stirred at low temperature for 20 to 30 minutes. Copper(I) iodide 42 mg, 0.22 mmol) was taken up in a separate predried round bottom flask and anhydrous tetrahydrofuran (4 mL) added to form a suspension of the copper iodide.

To this suspension was then added tri-n-butyl phosphine (117 µL, 0.47 mmol) and the mixture stirred at room temperature for one hour. The resulting homogenous colorless solution was then cooled to 0° C and transferred to the above organolithium reagent prepared using a cannula at -78° C. The reaction medium was then stirred for the next 15 to 20 minutes. The ongoing intermediate triflate synthon (114 mg, 0.213 mmol) was taken up in anhydrous tetrahydrofuran under a blanket of purified argon and transferred to the above cuprate reagent at -78°C. The resulting dark reaction solution was stirred for 15 hours and then quenched with saturated ammonium chloride solution. The organic soluble portion was then taken up in chloroform (25 mL). The aqueous portion was then repeatedly extracted with chloroform (25 mL X 3). The combined organic portion was then dried over with anhydrous sodium sulfate, filtered and concentrated to yield the desired product in the crude form. The crude form was then flash chromatographed over a bed of silica gel using 10% methanol in chloroform to obtain the title compound in 75% yield.

^{1}H NMR (300 MHz; $CDCl_3$): 0.645 δ (9H, s); 0.90 δ (3H, t, J= 5.4 Hz); 2.12 δ (2H, q, J= 7.2 Hz); 2.21 δ (3H, s); 2.23 δ (3H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.49 δ (2H, q, J= 2.5 Hz); 7.12 δ (1H, s); 7.87 δ

(1H, t, J= 7.2 Hz); 7.95 δ (1H, t, J= 7.9 Hz); 8.21 δ (1H, d, J= 5.4 Hz); 8.27 δ (1H, d, J= 5.2 Hz)

^{13}C NMR: δ 1.03, 7.58, 30.23, 51.7, 65.23, 72.36, 96.43, 96.43, 118.88, 127.51, 128.31, 128.70, 129.69, 130.48, 131.44, 135.95, 143.46, 145.42, 147.20, 150.15, 156.74, 172.58

FAB-MS: 464 (M+1)

EXAMPLE 22

7-(trimethylsilyl)camptothecin

20-O-acetyl-7-(trimethylsilyl)camptothecin (100 mg, 0.21 mmols) was dissolved in reagent grade methanol (20 mL) and aqueous potassium carbonate (25 mg in 0.1 mL water) was added and the mixture stirred for about 3 hours at room temperature. The resulting reaction mixture was then cooled to 5° C and acidified with 1N HCl to precipitate the lactone form of the compound. The precipitated product was then filtered, washed with water (10 mL X 4) and with ether (10 mL), and dried under vacuum. The pale yellow powder was then analyzed to the desired product (60 mg; 63%).

^{1}H NMR (300 MHz; $CDCl_3$): 0.645 δ (9H, s); 0.90 δ (3H, t, J= 5.4 Hz); 2.12 δ (2H, q, J= 7.2 Hz); 2.23 δ (3H, s); 3.6 δ (1H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.49 δ (2H, q, J= 2.5 Hz); 7.12 δ (1H, s); 7.87 δ (1H, t, J= 7.2 Hz); 7.95 δ (1H, t, J= 7.9 Hz); 8.21 δ (1H, d, J= 5.4 Hz); 8.27 δ (1H, d, J= 5.2 Hz)

^{13}C NMR: δ 1.03, 7.58, 30.23, 51.7, 65.23, 72.36, 96.43, 96.43, 118.88, 127.51, 128.31, 128.70, 129.69, 130.48, 131.44, 135.95, 143.46, 145.42, 147.20, 150.15, 156.74, 172.58

FAB-MS: 421 (M+1)

EXAMPLE 23

20-O-acetyl-7-[(β-trimethylsilyl)ethynyl]camptothecin

The 20-O-acetyl-7-triflate (100 mg, 0.1855 mmol) was dissolved in anhydrous and degassed anhydrous dimethylformamide (5 mL) and zinc chloride (50.5 mg, 0.371 mmol) added. To it was then added tris(dibenzylideneacetonyl)bis palladium(0) (17 mg, 0.371 mmol) followed by tri(2-furyl)phosphine (20 mg, 0.074 mmol). The resulting solution was stirred for approximately 30 minutes at room temperature. Then was added acetylenic trimethylsilane (0.1 mL). The reaction mixture was then stirred at room temperature for 48 hours. The resulting dark brown colored reaction mixture was then diluted with methylene chloride (25 mL), filtered, washed with water (15 mL). The crude product obtained after concentration was then flashed through a columnar bed of "Florisil", the fractions pooled, concentrated, dried under vacuum and analyzed.

^1H NMR (300 MHz; $CDCl_3$): 0.45 δ (9H, s); 0.87 δ (3H, t, J= 5.4 Hz); 1.85 δ (2H, q, J= 7.2 Hz); 2.31 δ (3H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, m); 7.07 δ (1H, s); 7.87 δ (1H, t, J= 7.2 Hz); 7.95 δ (1H, t, J= 7.9 Hz); 8.21 δ (1H, d, J= 8.4 Hz); 8.27 δ (1H, d, J= 6.2 Hz)

FAB-MS (M+1): 501

EXAMPLE 24

20-O-acetyl-7-ethynylcamptothecin

20-O-acetyl-7-(trimethylsilyl)camptothecin (100 mg, 0.21 mmols) was dissolved in reagent grade methanol (20 mL) and aqueous potassium carbonate (25 mg in 0.1 mL water) added and the mixture stirred for about 15 minutes at low temperature. The resulting reaction mixture was then cooled to 5° C and acidified with 1N HCl to precipitate the lactone form of the compound. The precipitated product was then filtered, washed with water (10 mL X 4) and with ether (10 mL), dried under vacuum.

The pale yellow powder was then analyzed to the desired product (40 mg; 53%).

^{1}H NMR (300 MHz; $CDCl_3$): 0.90 δ (3H, t, J= 5.4 Hz); 2.12 δ (2H, q, J= 7.2 Hz); 2.23 δ (3H, s); 3.6 δ (1H, s); 4.06 δ (1H, s); 5.42 d (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.49 δ (2H, q, J= 2.5 Hz); 7.12 δ (1H, s); 7.87 δ (1H, t, J= 7.2 Hz); 7.95 δ (1H, t, J= 7.9 Hz); 8.21 δ (1H, d, J= 5.4 Hz); 8.47 δ (1H, d, J= 5.2 Hz)

EXAMPLE 25

7-Ethynylcamptothecin

20-O-acetyl-7-ethynylcamptothecin (50 mg, 0.11 mmols) was dissolved in reagent grade methanol (5 mL) and aqueous potassium carbonate (25 mg in 0.1 mL water) added and the mixture stirred for about 2 hours at low temperature. The resulting reaction mixture was then cooled to 5° C and acidified with 1N HCl to precipitate the lactone form of the compound. The precipitated product was then filtered, washed with water (10 mL X 4) and with ether (10 mL), dried under vacuum. The pale yellow powder was then analyzed to the desired product (60 mg; 63%).

^{1}H NMR (300 MHz; $CDCl_3$): 0.90 δ (3H, t, J= 5.4 Hz); 2.12 δ (2H, q, J= 7.2 Hz); 3.6 δ (1H, s); 4.06 δ (1H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.49 δ (2H, q, J= 2.5 Hz); 7.12 δ (1H, s); 7.87 δ (1H, t, J= 7.2 Hz); 7.95 δ (1H, t, J= 7.9 Hz); 8.21 δ (1H, d, J= 5.4 Hz); 8.47 δ (1H, d, J= 5.2 Hz)

EXAMPLE 26

7-[(β-trimethylsilyl)ethyl]camptothecin

Camptothecin (500 mg, 1.44 mmols) was suspended in deionized water (10 mL) and freshly distilled 3-trimethylsilyl-1-propanal (3.0 mL; excess), followed by dropwise addition of concentrated sulfuric acid (5.5 mL)

at 0° C using an ice bath over a period of 15 min. To the above stirred reaction medium was then introduced 30% aqueous solution of hydrogen peroxide (2 mL) followed by iron sulfate heptahydrate (156 mg) in 1 mL water. The reaction mixture was then stirred at 25° C for an additional 24 hours. The reaction mixture was then diluted with ice-cold water and extracted with chloroform (50 mL X 3). The combined organic portion was then dried over anhydrous sodium sulfate, filtered and concentrated to obtain the crude product in 65% yield. The crude product was then purified over a silica gel column using 90% chloroform-methanol mixture to furnish 0.46 g of the title compound (54% yield).

^{1}H NMR (300 MHz; $CDCl_3$): 0.01 δ (9H, s); 0.48 δ (2H, q, J= 4.8 Hz); 0.90 δ (3H, t, J= 5.4 Hz); 1.53 δ (2H, q, J= 6.6 Hz); 2.12 δ (2H, q, J= 7.2 Hz); 2.23 δ (3H, s); 3.6 d (1H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.49 δ (2H, q, J= 2.5 Hz); 7.12 δ (1H, s); 7.87 δ (1H, t, J= 7.2 Hz); 7.95 δ (1H, t, J= 7.9 Hz); 8.21 δ (1H, d, J= 5.4 Hz); 8.27 δ (1H, d, J= 5.2 Hz)

^{13}C NMR: δ 1.03, 7.58, 9.62, 23.48, 30.23, 51.7, 65.23, 72.36, 96.43, 96.43, 118.88, 127.51, 128.31, 128.70, 129.69, 130.48, 131.44, 135.95, 143.46, 145.42, 147.20, 150.15, 156.74, 172.58

FAB-MS: 492 (M+1)

EXAMPLE 27

<u>20-O-acetyl-7-[(β-trimethylsilyl)ethylthio]camptothecin</u>

The intermediate triflate (100 mg, 0.186 mmol) was dissolved in anhydrous 1,4-dioxane and cooled to 0° C under a stream of argon. To it was then added diisopropyl ethylamine (0.1 mL; 0.557 mmole) and trimethylsilyl ethanethiol (0.25mL) was slowly added and then the reaction mixture was stirred under a balloon

pressure of argon for 15 hours in a well ventilated hood. After 15 hours, the reaction mixture was diluted with methylene chloride (25 mL) and washed with water (20 mL X 4), dried over anhydrous sodium sulfate, filtered and concentrated to obtain the crude product of the title compound in approximately 80% yield.

^{1}H NMR (300 MHz; $CDCl_3$): 0.01 δ (9H, s); 0.87 δ (3H, t, J= 5.4 Hz); 0.98 δ (2H, q, J= 4.8 Hz); 1.26 δ (3H, t, J= 5.8 Hz); 1.89 δ (2H, q, J= 7.2 Hz); 2.31 δ (3H, s); 2.28 d (3H, s); 3.05 δ (2H, q, J= 5 Hz); 3.19 δ (2H, q, J= 7.2 Hz); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, s); 7.07 δ (1H, s); 7.65 δ (1H, t, J= 7.2 Hz); 7.75 δ (1H, t, J= 7.9 Hz); 8.1 δ (1H, d, J= 8.4 Hz); 8.58 δ (1H, d, J= 6.2 Hz)

FAB-MS: 523(M+1)

EXAMPLE 28

7-[(β-Trimethylsilyl)ethylthio]camptothecin

20-O-acetyl-7-(ethylthio)camptothecin (100 mg, 0.21 mmols) was dissolved in reagent grade methanol (20 mL) and aqueous potassium carbonate (25 mg in 0.1 mL water) added and the mixture stirred for about 3 hours at low temperature. The resulting reaction mixture was acidified with 1N HCl to precipitate the lactone form of the compound. The precipitated product was then filtered, washed with water (10 mL X 4) and with ether (10 mL) and dried under vacuum. The pale yellow powder was then analyzed to the desired product (69 mg; 76%).

^{1}H NMR (300 MHz; $CDCl_3$): 0.01 δ (9H, s); 0.87 δ (3H, t, J= 5.4 Hz); 0.98 δ (2H, q, J= 4.8 Hz); 1.26 δ (3H, t, J= 5.8 Hz); 1.89 δ (2H, q, J= 7.2 Hz); 2.31 δ (3H, s); 2.28 δ (3H, s); 3.05 δ (2H, q, J= 5 Hz); 3.19 δ (2H, q, J= 7.2 Hz); 3.6 δ (1H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, s); 7.07 δ (1H, s); 7.65 δ (1H, t, J= 7.2

Hz); 7.75 δ (1H, t, J= 7.9 Hz); 8.1 δ (1H, d, J= 8.4 Hz); 8.58 δ (1H, d, J= 6.2 Hz)

FAB-MS: 481 (M+1)

EXAMPLE 29

20-O-acetyl-7-[(trimethylsilyl)methylthio]camptothecin

The intermediate triflate (100 mg, 0.186 mmol) was dissolved in anhydrous 1,4-dioxane (2 mL) and cooled to 0° C under a stream of argon. To it was then added diisopropyl ethylamine (0.1 mL; 0.557 mmole) and (trimethylsilyl)methanethiol (0.2mL) slowly added and then the reaction mixture stirred under a balloon pressure of argon for 15 hours in a well ventilated hood. After 48 hours, the reaction mixture was diluted with methylene chloride (25 mL) and washed with water (20 mL X 4), dried over anhydrous sodium sulfate, filtered and concentrated to obtain the crude product of the title compound in approximately 70% yield.

^{1}H NMR (300 MHz; $CDCl_3$): 0.15 δ (9H, s); 0.87 δ (3H, t, J= 5.4 Hz); 1.26 δ (3H, t, J= 5.8 Hz); 2.21 δ (3H, s); 2.19 δ (2H, q, J= 7.2 Hz); 2.31 δ (2H, s); 2.38 δ (2H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, s); 7.07 δ (1H, s); 7.65 d (1H, t, J= 7.2 Hz); 7.75 d (1H, t, J= 7.9 Hz); 8.22 δ (1H, d, J= 8.4 Hz); 8.55 δ (1H, d, J= 6.2 Hz)

FAB-MS: 509(M+1)

EXAMPLE 30

7-[(Trimethylsilyl)methylthio]camptothecin

20-O-acetyl-7-(methylthio)camptothecin (100 mg, 0.21 mmols) was dissolved in reagent grade methanol (20 mL) and aqueous potassium carbonate (25 mg in 0.1 mL water) added and stirred for about 3 hours at low temperature. The resulting reaction mixture was acidified with 1N HCl to precipitate the lactone form of the compound. The precipitated product was then filtered, washed with water (10 mL X 4) and with ether (10 mL), dried under vacuum.

The pale yellow powder was then analyzed to the desired product (59 mg; 67%).

^{1}H NMR (300 MHz; $CDCl_3$): 0.15 δ (9H, s); 0.87 δ (3H, t, J= 5.4 Hz); 1.26 δ (3H, t, J= 5.8 Hz); 2.19 δ (2H, q, J= 7.2 Hz); 2.28 δ (2H, s); 2.38 δ (2H, s); 3.6 δ (1H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, s); 7.07 δ (1H, s); 7.65 δ (1H, t, J= 7.2 Hz); 7.75 δ (1H, t, J= 7.9 Hz); 8.1 δ (1H, d, J= 8.4 Hz); 8.58 δ (1H, d, J= 6.2 Hz)

FAB-MS: 467 (M+1)

EXAMPLE 31

<u>20-deoxycamptothecin (used in Example 37)</u>

Camptothecin (500 mg, 1.44 mmol) was suspended in 1,4-dioxane (10 mL) and Lawsson's reagent (290.5 mg, 0.72 mmol) added. The reaction mixture was then heated to 90° C for 10 hours under an inert atmosphere. The resultant homogeneous reaction mixture was then concentrated, organic portion was taken up in chloroform (25 mL) and the aqueous fraction was repeatedly extracted with chloroform (25 mL X 3). The combined organic portion was then concentrated to get the title compound in the crude form. The crude product was then flash chromatographed over a bed of "Florisil" using 10% chloroform in methanol to furnish the desired product in 40% yield in diastereomeric mixture.

^{1}H NMR (300 MHz; $CDCl_3$): 1.07 δ (3H, t, J= 5.4 Hz); 2.12 δ (2H, q, J= 7.2 Hz); 3.69 δ (1H, t, J= 6.6 Hz); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.59 δ (2H, q, J= 2.5 Hz); 7.62 δ (1H, s); 7.71 δ (1H, t, J= 7.2 Hz); 7.85 δ (1H, t, J= 7.9 Hz); 8.01 δ (1H, d, J= 5.4 Hz); 8.23 δ (1H, d, J= 5.2 Hz); 8.47 δ (1H, s)

^{13}C NMR: δ 11.1, 25.25, 29.6, 45.81, 49.93, 66.04, 99.76, 120.79, 128.10, 128.24, 128.72, 129.8, 130.73, 131.2, 146.12, 147.27, 149.06, 158.01 and 171.01

FAB-MS (M+1): 361.2

EXAMPLE 32

20-(Methanesulfonyl)camptothecin (used in Example 33)

To a suspension of camptothecin (2.0 g, 5.7 mmol) in 100 mL dichloromethane was added 20 mL pyridine, and 6.5 mL methanesulfonyl chloride. The mixture was stirred at room temperature under nitrogen for 3 days. It turned to homogeneous solution. Solvents were removed by high vacuum. The residue was purified by flash column chromatography, eluted with ethyl acetate. 1.135g 20-mesylcamptothecin was obtained, 46% yield.

^{1}H NMR ($CDCl_3$) 8.38 δ (1H, s), 8.23 δ (1H, d, J= 8.7 Hz), 7.91 δ (1H, d, J= 8.1 Hz), 7.82 δ (1H, t, J= 8.4 Hz), 7.66 δ (1H, t, J= 7.8 Hz), 7.62 δ (1H, s), 5.64 δ (1H, d, J= 17.7 Hz), 5.36 δ (1H, d, J= 17.7 Hz), 5.29 δ (2H, s), 3.32 δ (3H, s), 2.29 δ (2H, m), 0.97 δ (3H, t, J= 7.5 Hz).

EXAMPLE 33

20-Deoxycamptothecin

To a solution of 20-mesylcamptothecin (0.59g, 1.38 mmol) in 30 dioxane was added 0.30g of sodium iodide and tributylstannyl hydride (0.90 mL, 2.5 equiv.). The mixture was heated to reflux for 4 hours. After cooling down to room temperature, the reaction mixture was diluted with 50 mL diethyl ether. The precipitate was filtered off. The mother liquor was then diluted with 50 mL of hexane. Precipitate was then combined with collected residue and dissolved in chloroform, washed with brine, dried over anhydrous sodium sulfate. The solvent was removed to provide 0.386g of 20-deoxycamptothecin, 69% yield.

^{1}H NMR ($CDCl_3$) 8.39 δ (1H, s), 8.22 δ (1H, d, J= 8.7 Hz), 7.91 δ (1H, d, J= 8.1 Hz), 7.83 δ (1H, t, J= 8.4 Hz), 7.66 δ (1H, t, J= 7.8 Hz), 7.18 δ (1H, s), 5.64 δ (1H, d, J= 16.5 Hz), 5.36 δ (1H, d, J= 16.5 Hz), 5.29 δ (2H, s), 3.62 δ (1H, t, J= 6.6 Hz), 2.09 δ (2H, m), 1.09 δ (3H, t, J= 7.5 Hz).

EXAMPLE 34

20-O-acetyl-7-[(γ-trimethylsilyl)-α-propenyl]camptothecin

The 20-O-acetyl-7-triflate (100 mg, 0.1855 mmol) was dissolved in anhydrous and degassed anhydrous dimethylformamide (5 mL) and zinc chloride (50.5 mg, 0.371 mmol) added. To it was then added tris(dibenzylideneacetonyl)bis palladium(0) (17 mg, 0.371 mmol) followed by tri(2-furyl)phosphine (20 mg, 0.074 mmol). The resulting solution was stirred for approximately 30 minutes at room temperature. Then was added propenylic trimethylsilane [(3-trimethylsilyl)-1-propene] (0.1 mL). The reaction mixture was then stirred at room temperature for 48 hours. The resulting dark brown colored reaction mixture was then diluted with methylene chloride (25 ml), filtered, washed with water (15 ml). The crude product obtained after concentration was then flashed through a columnar bed of "Florisil", the fractions pooled, concentrated, dried under vacuum and analyzed.

^{1}H NMR (300 MHz; $CDCl_3$): 0.26 δ (9H, s); 0.97 δ (3H, t, J= 5.4 Hz); 2.02 δ (2H, s); 2.24 δ (2H, q, J= 7.2 Hz); 2.21 δ (3H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, m); 7.2 δ (1H, s); 7.77 δ (1H, t, J= 7.2 Hz); 7.85 δ (1H, t, J= 7.9 Hz); 8.21 δ (1H, d, J= 8.4 Hz); 8.32 δ (1H, d, J= 6.2 Hz)

FAB-MS (M+1): 501

EXAMPLE 35

20-O-acetyl-7-(α-propenyl)camptothecin

20-O-acetyl-7-[(γ-trimethylsilyl)propen-α-yl]camptothecin (100 mg, 0.21 mmols) was dissolved in reagent grade methanol (20 mL) and aqueous potassium carbonate (25 mg in 0.1 mL water) added and the mixture stirred for about 15 minutes at low temperature. The resulting reaction mixture was then cooled to 5° C and acidified with 1N HCl to precipitate the lactone form of the compound. The precipitated product was then filtered, washed with water (10 mL X 4) and with ether (10 mL), dried under vacuum. The pale yellow powder was then analyzed to the desired product (40 mg; 53%).

^{1}H NMR (300 MHz; $CDCl_3$): 0.97 δ (3H, t, J= 5.4 Hz); 2.02 δ (2H, s); 2.24 δ (2H, q, J= 7.2 Hz); 2.21 δ (3H, s); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, m); 7.2 δ (1H, s); 7.77 δ (1H, t, J= 7.2 Hz); 7.85 δ (1H, t, J= 7.9 Hz); 8.21 δ (1H, d, J= 8.4 Hz); 8.32 δ (1H, d, J= 6.2 Hz)

EXAMPLE 36

7-[(γ-trimethylsilyl)-α-propenyl]camptothecin

20-O-acetyl-7-[(γ-trimethylsilyl)-α-propenyl]camptothecin (50 mg, 0.11 mmols) was dissolved in reagent grade methanol (5 mL) and aqueous potassium carbonate (25 mg in 0.1 mL water) added and the mixture stirred for about 2 hours at low temperature. The resulting reaction mixture was then cooled to 5° C and acidified with 1N HCl to precipitate the lactone form of the compound. The precipitated product was then filtered, washed with water (10 mL X 4) and with ether (10 mL), dried under vacuum. The pale yellow powder was then analyzed as the desired product (60 mg; 63%), i.e. CPT-7-CH=CH-CH_2-TMS and 10% of the isomerized congener, the corresponding 7-allenic derivative, 7-[(γ-trimethylsilyl)-α,β-propadienyl]camptothecin, i.e. CPT-7-CH=C=CH-TMS.

NMR spectrum for the major product was as follows: ^{1}H NMR (300 MHz; $CDCl_3$): 0.26 δ (9H, s); 0.97 δ (3H, t, J= 5.4 Hz); 2.02 δ (2H, s, corresponds to the acetylenic counterpart); 2.24 δ (2H, q, J= 7.2 Hz); 5.42 δ (2H, ABq, J^1= 17.5 Hz; J^2= 6.1 Hz); 5.61 δ (2H, m); 7.2 δ (1H, s); 7.77 δ (1H, t, J= 7.2 Hz); 7.85 δ (1H, t, J= 7.9 Hz); 8.21 δ (1H, d, J= 8.4 Hz); 8.32 δ (1H, d, J= 6.2 Hz)

EXAMPLE 37

7-[(β-trimethylsilyl)ethyl]-20-deoxycamptothecin

20-Deoxycamptothecin (200 mg) was suspended in 10 mL of water and to it was added ferrous sulfate heptahydrate (400 mg), followed by glacial acetic acid (5 mL). The above reaction mixture was stirred for 15 minutes and then concentrated sulfuric acid (4 mL) was added dropwise, maintaining the reaction temperature around 15°C. Finally, 30% hydrogen peroxide (0.2 mL) was added to the above reaction mixture and the mixture stirred at room temperature for 3 hours. The organic portion was then taken up in chloroform. The aqueous portion was then repeatedly extracted with chloroform (50 mL X 5). The combined organic fraction was then washed with water, brine and then dried over anhydrous sodium sulfate. The product-containing portion was then filtered and evaporated to obtain 120 mg of the desired product in the crude form. The crude product was then chromatographed over silica gel using ethyl acetate-chloroform mixture to furnish the title compound (85 mg).

^{1}H NMR ($CDCl_3$) 8.39 δ (1H, s), 8.22 δ (1H, d, J = 8.7 Hz), 7.91 δ (1H, d, J = 8.1 Hz), 7.83 δ (1H, t, J = 8.4 Hz), 7.66 δ (1H, t, J = 7.8 Hz), 7.18 δ (1H, s), 5.64 δ (1H, d, J = 16.5 Hz), 5.36 δ (1H, d, J = 16.5 Hz), 5.29 δ (2H, s), 3.62 δ (1H, t, J = 6.6 Hz), 2.09 δ (2H, m), 1.09 δ (3H, t, J = 7.5 Hz)and 0.12 δ (9H, s).

EXAMPLE 38

20-O-acetylocamptothecin

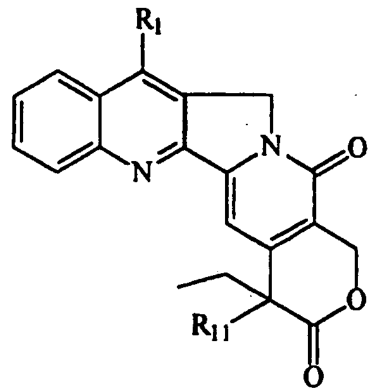
Camptothecin (2 grams, 5.7 mmols) was dissolved in anhydrous pyridine (30 ml) and acetic anhydride (15 ml) slowly added maintaining the exothermicity of the reaction. The reaction was then stirred for 30 minutes and then catalytic amounts of dimethyl aminopyridine (approximately 70 mg) were added and the reaction continued to completion during 12-15 hours at room temperature. The product was then precipitated out by pouring the reaction mixture into crushed ice. The precipitate was then filtered and washed with cold water followed by cold ether. The final purification was best done by a flash chromatography of the above product over silica gel matrix using chloroform as the eluant to obtain the title compound in 85% yield.

1H NMR (300 MHz; d6-DMSO): 0.87δ (3H, t, J=5.4Hz); 2.12δ (2H, q, J=7.2Hz); 2.21δ (3H, s);5.42δ(2H, ABq, J^1=17.5Hz; J^2=6.1Hz);5.49δ (2H, q, J=2.5Hz); 7.14δ (1H,s); 7.97δ (1H, t, J=7.2Hz); 8.05δ (1H, t, J=7.9Hz); 8.12δ (1H, d, J=8.4Hz); 8.35δ (1H, d, J=6.2Hz) and 8.45δ (1H, s)
FAB-MS;391(M+1)

The above procedure was used to prepare 20-O-acetylcamtothecinone from camptothecinone and 20-O-acetylcamptothecin-1-oxide from camptothecin-1-oxide. These compounds were used in Examples 4 and 5.

CLAIMS

1. Compounds having the formula (I):



(I)

wherein:

- R_1 is acyl of formula $-C(O)R_2$ wherein R_2 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl or aryl; or R_1 is C_{2-8} alkenyl or C_{2-8} alkynyl, each of which is optionally substituted by one or more halogen atoms, hydroxy groups, C_{1-6} alkyl or C_{1-6} alkoxy groups; or R_1 is halo; oxo, in which case the 1,2- and 6,7-ring double bonds are replaced by a single 2,6-ring double bond; or $-S-R_3$, wherein R_3 is C_{1-6} alkyl, aryl or halo- or C_{1-6} alkyl-substituted aryl; or R_1 is $-S(O)-C_{1-6}$ alkyl; $-OSO_2CF_3$; or $-SiR_8R_9R_{10}$, $-R_5-SiR_8R_9R_{10}$ or $-S-R_5-SiR_8R_9R_{10}$ wherein R_5 is C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene and each of R_8, R_9 and R_{10} is individually hydrogen or C_{1-6} alkyl; and
- R_{11} is hydrogen, hydroxy or a hydroxy-protecting group which protects the hydroxy group against triflylation;

in the form of the free bases or pharmaceutically acceptable acid addition salts thereof.

2. Compounds according to Claim 1 wherein R_1 is an acyl group; halo; a said substituted or unsubstituted C_2-C_8 alkenyl or C_2-C_8 alkynyl group; $-S-R_3$; $-S(O)-C_{1-6}$ alkyl;

or a said or $-SiR_8R_9R_{10}$, $-R_5-SiR_8R_9R_{10}$ or $-S-R_5-SiR_8R_9R_{10}$ group; and

R_{11} is hydrogen or hydroxy.

3. Compounds according to Claim 1 or 2, wherein R_8, R_9 and R_{10} are all methyl groups.

4. Compounds according to Claim 3, wherein R_1 is $-C_{1-6}$-alkylene-$Si(CH_3)_3$ or S-C_{1-6}-alkylene-$Si(CH_3)_3$.

5. Compounds according to Claim 4, wherein R_1 is β-(trimethylsilyl)ethyl.

6. Compounds according to Claim 4, wherein R_1 is (trimethylsilyl)methyl.

7. Compounds according to Claim 4, wherein R_1 is trimethylsilyl.

8. Compounds according to Claim 4, wherein R_1 is (trimethylsilyl)ethenyl.

9. Compounds according to Claim 4, wherein R_1 is (trimethylsilyl)ethynyl.

10. Compounds according to Claim 1, wherein R_1 is trifluoromethylsufonyloxy.

11. A pharmaceutical formulation comprising a compound defined in Claim 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, in association with one or more pharmaceutically acceptable excipients, carriers or diluents.

12. Compounds according to Claim 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, and a formulation according to Claim 11 for treating patients with cancer.

13. Use of a compound according to 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, in the preparation of a medicament for treating patients with cancer.

INTERNATIONAL SEARCH REPORT

Interna. al Application No
PCT/GB 97/02205

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D491/22 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	DE 25 34 601 A (BASF) 17 February 1977 see whole document ---	1,2, 11-13
X	DE 21 50 234 A (BASF) 12 April 1973 see whole document ---	1,2, 11-13
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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1

Date of the actual completion of the international search	Date of mailing of the international search report
25 November 1997	10.12.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,	

INTERNATIONAL SEARCH REPORT

Intern. ...al Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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